PROCEEDINGS
of the
XXXI National Continuing
Medical Education Programme
In Surgery

SURGERY UPDATE 2014

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FOREWORD

The National Continuing Medical Education Programme in Surgery organized by the department of Surgery, Maulana Azad Medical College, New Delhi is in its twenty ninth year of existence. During this period has blossomed into a six day academic exercise eagerly looked forward to by the surgeons all over the country and has established itself as the gold standard for Continuing Medical Education Programmes. One of its endearing features is the CME lectures brought out in a bound format simply named the **PROCEEDINGS,** introduced and published in 1998 The PROCEEDINGS have become an integral part of the update since then. It is satisfying to note that the bound lectures are carried by postgraduates all over the country preparing for examinations or for interviews. Those who miss out on attending the CME programme, still manage to procure copies of the PROCEEDINGS in its photocopied form. This year also it gives us great pleasure to present a book on the **PROCEEDINGS OF THE XXXI NATIONAL CONTINUING MEDICAL EDUCATION PROGRAMME IN SURGERY**, similar to previous years.

Every surgical disorder in the scientific programme has been chosen carefully in the context of its importance to the attending delegates. All the authors are well-recognized authorities with a vast personal clinical experience on the particular subject they were chosen to elaborate. As will be evident from the written texts, they have contributed a very comprehensive account of the respective topics and are also to be commended for submitting the latest references at the end of each chapter for ready referral. The quality of their text reflects their involvement in our programme. A sincere effort has been made to format the book in a uniform manner without any effort to edit the text provided by the contributors.

This year's programme is a full day comprehensive CME on selected topics of particular interest to the postgraduate. Emphasis is on subjects with more bearing on their clinical application. Every year's Proceedings can be considered one part of the trilogy of books which will cover nearly the whole course for the postgraduate student over a three year period.

We sincerely thank the contributors for their effort. We also wish to thank all the colleagues in the department for their encouragement and guidance in making this project possible. Especial thanks are to Prof. Rajdeep Singh, who has been instrumental in collecting the articles and majorly formatting the text to its final form. Our sincere thanks are also due to the resident staff who worked for procuring, proof reading and formatting the text. Finally, we must emphasize the contribution of the authors who have always given an overwhelming response to our endeavor of bringing out the written text of our CME programme over the years. We sincerely hope that the Proceedings will meet the stiff demands of the delegates and serve as a nodal point of learning for the postgraduates.

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SURGERY UPDATE 2014

सरस्वती वन्दना

PRAYER TO SARASWATI, THE GODDESS OF LEARNING

मन के हजारो द्वार पथ गलीयार सब उजीयार दे
जीवन जगत् को ज्योती का उपहार दे मॉ शारदे।

**MAN KE HAZAARON DVAARA PATHA GALIYAARA SABA UJIYAARA DE,
JEEVAN JAGAT KO JYOTI KAA UPAHAARA DE MAA SHAARADE.**

O! Goddess of learning, Mother Shaaradaa, bestow upon the whole living world
Your blissful light. May our thoughts and minds be illuminated by your knowledge.

जल उठे तेरे भवन मे आज कितने दीप पावन
भाव चिन्तन के महकते फूल अक्षत् धूप चन्दन
कल्पनाओ को सदा आधार दे आकार दे ओ शारदे।

**JALA UTHE TERE BHAVANA MEIN AAJ KITANE DEEPA PAAVANA
BHAVA CHINTANA KE MAHAKATE PHOOLA AKSHAT DHOOPA CHANDANA
KALPANAAON KO SADAA AADHAARA DE, AAKAARA DE, O SHAARADE.**

So many lamps (of writings) have been lighted in your service. Our love towards you is expressed in
Our creative writings which are as if offerings of flowers, unbroken rice, essence and sandal to you.
We pray to you, O Goddess, that you always be kind enough to give our thoughts a direction and
Sense of constructiveness.

वीणाधरा श्वेताम्बर शूभ भाव प्रेरक उज्जवला
मानव कमल विकसित करो ओ पुश्प पावन मॅगला
जन चेतना के पर्त्त सब करूणामयी झॅकार दे ओ शारदे।

**VEENADHARAA SWETAAMBARAA SHUBHA BHAAVA PRERAKA UJJWALAA
MAANSA KAMLA VIKASITA KARO PUNYA PAAWANA MANAGALAA
JANA CHETANAA KE PARTTA SABA KARUNAA MAYEE JHANKAAR DE, O SHAARADE.**

O Goddess! Your ways are soft and musical, so they touch the soul. You are purity within and
without, hence you may drive us to purity and universal welfare. O Goddess! I entreat upon you
again and again that you nourish our mind and in it a deep and pure sense of good for all. You are
blissful, you are pure, you are meritorious, therefore, you will let our conscience and ideas vibrate
with your essence and make them beautiful.

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Complications of Haemorrhoidectomy

Gulshanjit Singh

Introduction

Within the normal anal canal there are specialized, highly vascularized cushions forming discrete masses of thick submucosa containing blood vessels, smooth muscle, and elastic and connective tissue. They are located in the left lateral, right anterior, and right posterior quadrants of the canal to aid in anal continence. The term hemorrhoids should be restricted to clinical situations in which these cushions are abnormal and cause symptoms. They may be no more than the downward sliding of anal cushions associated with gravity, straining, and irregular bowel habits.

Signs and Symptoms

Hemorrhoids can be considered external or internal; the diagnosis is based on the history, physical examination, and endoscopy. External hemorrhoids are covered with anoderm and are distal to the dentate line; they may swell, causing discomfort and difficult hygiene, but cause severe pain only if actually thrombosed. Internal hemorrhoids cause painless, bright red bleeding or prolapse associated with defecation. A skin tag is redundant fibrotic skin at the anal verge, often persisting as the residua of a thrombosed external hemorrhoid. Postpartum hemorrhoids result from straining during labor, which results in edema, thrombosis, and/or strangulation.

Portal hypertension was long thought to increase the risk of hemorrhoidal bleeding because of the anastomoses between the portal venous system (middle and upper hemorrhoidal plexuses) and the systemic venous system (inferior rectal plexuses). It is now understood that hemorrhoidal disease is no more common in patients with portal hypertension than in the normal population. Rectal varices, however, may occur and may cause hemorrhage in these patients. In general, rectal varices are best treated by lowering portal venous pressure. Rarely, suture ligation may be necessary if massive bleeding persists. Surgical hemorrhoidectomy should be avoided in these patients because of the risk of massive, difficult-to-control variceal bleeding.

Internal hemorrhoids are classified according to the extent of prolapse, which influences treatment options

Grade	Symptoms and signs	Management
First degree	Bleeding; no prolapse	Dietary modifications
Second degree	Prolapse with spontaneous reduction Bleeding, seepage	Rubber band ligation Coagulation Dietary modifications
Third degree	Prolapse requiring digital reduction Bleeding, seepage	Surgical hemorrhoidectomy Rubber band ligation Dietary modifications
Fourth degree	Prolapsed, cannot be reduced Strangulated	Surgical hemorrhoidectomy Urgent hemorrhoidectomy Dietary modifications

Treatment

Depending on the degree of disease, treatment falls into two main categories, nonsurgical and hemorrhoidectomy.

Nonoperative Management

Nonoperative Management In many patients, hemorrhoidalsymptoms can be ameliorated or relieved by simple measures,such as better local hygiene, avoidance of excessive straining, andbetter dietary habits supplemented by medication to keep stoolssoft, formed, and regular. Symptoms ofbleeding but not prolapse can be significantly reduced over aperiod of 30 to 45 days with the use of fiber supplements.

Operative Management

1.Rubber Band Ligation

In the absence of symptomatic external hemorrhoids, second- and some third-degree internal hemorrhoids can be treated with office procedures that produce mucosal fixation. After firing the

ligator, the rubber band strangulates the underlying tissue, causing scarring and preventing further bleeding or prolapse With one or more applications, symptoms are alleviated in 79% of patients.

2.Infrared Photocoagulation
Infrared photocoagulation is an effective treatment for small first- and second-degree hemorrhoids. The instrument is applied to the apex of each hemorrhoid to coagulate the underlying plexus. All three quadrants may be treated during the same visit. Larger hemorrhoids and hemorrhoids with a significant amount of prolapse are not effectively treated with this technique.

3.Sclerotherapy
One to 3 mL of a sclerosing solution (phenol in olive oil, sodium morrhuate, or quinine urea) are injected into the submucosa of each hemorrhoid. Few complications are associated with sclerotherapy, but infection and fibrosis have been reported.

4.Excision of Thrombosed External Hemorrhoids
Acutely thrombosed external hemorrhoids generally cause intense pain and a palpable perianal mass during the first 24 to 72 hours after thrombosis. The thrombosis can be effectively treated with an elliptical excision under local anesthesia. Because the clot is usually loculated, simple incision and drainage is rarely effective. After 72 hours, the clot begins to resorb, and the pain resolves spontaneously. Excision is unnecessary, but sitz baths and analgesics often are helpful.

5.Surgical Hemorrhoidectomy
Whenever patients fail to respond satisfactorily to repeated attempts at conservative measures, hemorrhoids are severely prolapsed and require manual reduction, hemorrhoids are complicated by strangulation or associated pathology, such as ulceration, fissure, or fistula, or hemorrhoids are associated with symptomatic external hemorrhoids or large anal tags.

Closed Haemorrhoidectomy (Parks or Ferguson)
It provides simultaneous excision of internal and external hemorrhoids. Anoderm is preserved to avoid the long-term complication of anal stenosis. Patients typically recover sufficiently to return to work within 1 to 2 weeks. All three hemorrhoidal cushions may be removed using this technique; however, care should be taken to avoid resecting a large area of perianal skin to avoid postoperative anal stenosis

Open Haemorrhoidectomy (Milligan and Morgan)
As an alternative to the closed technique, the surgical wounds can be left open to reduce postoperative pain, but at the expense of longer healing times.

Whitehead's Hemorrhoidectomy
Whitehead's hemorrhoidectomy involves circumferential excision of the hemorrhoidal cushions just proximal to the dentate line. After excision, the rectal mucosa is then advanced and sutured to the dentate line. Most have abandoned this approach because of the risk of ectropion (Whitehead's deformity).

Harmonic Scalpel and LigaSure
Remove the excess hemorrhoidal tissue and coagulate or seal the blood vessels simultaneously, with minimal lateral thermal injury to nearby tissue. Reduction in trauma to the surrounding anal canal mucosa and underlying anal sphincter decrease postoperative edema and pain.

Procedure for Prolapse and Hemorrhoids/Stapled Hemorrhoidectomy
It was first described by Longo. Procedure for prolapse and hemorrhoids (PPH) has been proposed as an alternative surgical approach. The term PPH has largely replaced stapled hemorrhoidectomy because the procedure does not involve excision of hemorrhoidal tissue, but instead fixes the redundant mucosa above the dentate line. PPH removes a short circumferential segment of rectal mucosa proximal to the dentate line using a circular stapler. This effectively ligates the venules feeding the hemorrhoidal plexus and fixes redundant mucosa higher in the anal canal.

A systematic review and meta-analysis of prospective randomized comparisons of stapled hemorrhoidopexy with conventional hemorrhoidectomy has been conducted. This review incorporated literature from 29 randomized clinical trials representing 2056 patients. It concluded that the stapled hemorrhoidopexy offers some short-term benefits over the conventional approach. The total incidence of complications was the same for both approaches but the stapled hemorrhoidopexy was associated with a higher rate of recurrent disease.

Complications of Rubber Band Ligation

1.Perineal sepsis: Preferably, only one site should be banded each time. Because severe perineal sepsis and even deaths have been reported after rubber band ligation, patients should be instructed to return to the emergency department if delayed or undue pain, inability to void, or a fever develops. Treatment includes debridement of necrotic tissue, drainage of associated abscesses, and broad-spectrum antibiotics

2.Risk for bleeding: It is preferable that patients not be taking antiplatelet or blood-thinning medications. Bleeding may occur approximately 7 to 10 days after rubber band ligation, at the time when the ligated pedicle necroses and sloughs. Bleeding is usually self limited, but persistent hemorrhage may require examination under anesthesia and suture ligation of the pedicle.

3.Sepsis: Subacute bacterial endocarditis prophylaxis is administered to patients at risk. Rubber band ligation should be avoided in immunodeficient patients.

4.Severe pain will occur if the rubber band is placed at or distal to the dentate line where sensory nerves are located.

5.Urinary retention: It occurs in approximately 1% of patients and is more likely if the ligation has inadvertently included a portion of the internal sphincter.

Complications of Hemorrhoidectomy

1. Postoperative pain
Early postoperative pain is reported to be lower after PPH than after manual hemorrhoidectomy. Pain may be induced by a low anastomosis at the level of the sensitive epithelium, if the purse string is carried out too close to the dentate line, either in the lower rectum or in the upper anal canal. In a large series of over 3500 patients pain was so severe as to require readmission in 1.6% of the cases. It requires analgesia usually with oral narcotics. NSAIDs, muscle relaxants, topical analgesics, and comfort measures, including sitz baths, are often useful as well.

Severe chronic proctalgia after PPH is rarely reported. The incidence of chronic pain ranges from 1.6% to 31% in the studies reporting this complication. The two studies that better characterized chronic pain reported it as either post-defecatory or accompanied by urgency. Chronic pain has been related to smooth muscle incorporation in the doughnut although it may be present without muscle incorporation. Chronic pain has also been attributed to persistent hemorrhoidal disease, sphincter spasm, rectal spasm or high anal resting pressures, suture dehiscence, anal fissure, anorectal sepsis or retained staples. Chronic pain may occur more frequently in males. Comparing long-term results of PPH and Milligan-Morgan procedure for fourth-degree piles, Mattana et al. found that 8% of patients who had stapled hemorrhoidopexy complained of spontaneous pain or pain during defecation vs. 0% of patients who underwent the Milligan-Morgan procedure, although this difference was not statistically significant.

Post-evacuatory pain may respond to oral nifedipine. Chronic proctalgia may otherwise be a severe problem which is difficult to manage, and represents the most frequent indication for reintervention after PPH (44% of the reoperated patients). A novel procedure called “agrapphectomy” (from French agrapphes = staples) involving the excision of the staple line and the manual refashioning of the anastomosis, has been advocated as effective by Wunderlich et al. A more conservative approach using transanal electrostimulation or transanal injections of steroids and local anesthetic may be also attempted.

2. Bleeding
Although a small amount of bleeding, especially with bowel movements, is to be expected, massive hemorrhage can occur after hemorrhoidectomy. Bleeding may occur in the immediate postoperative

period (often in the recovery room) as a result of inadequate ligation of the vascular pedicle. This type of hemorrhage mandates an urgent return to the operating room where suture ligation of the bleeding vessel will often solve the problem. Bleeding mayalso occur 7 to 10 days after hemorrhoidectomy when the necrotic mucosa overlying the vascular pedicle sloughs. Although some of these patients may be safely observed, others will require an examination under anesthesia to ligate the bleeding vessel or to oversew the wounds if no specific site of bleeding is identified. According to a meta-analysis that analyzed 15 prospective randomized trials, the hemorrhoidopexy: hemorrhoidectomy ratio of postoperative rectal bleeding was 2.3:1. Bleeding is more likely to occur after PPH for fourth-degree hemorrhoids (11%), for anorectal varices (25%), and for thrombosed hemorrhoids (67%).

Four factors may help to minimize the risk of bleeding: manual overstitching of the staple line; use of gun, which has a smaller staple closure and is more hemostatic; tightening the gun to the absolute limit; and use of a postoperative endoanal sponge. The bleeding rate decreased from 12.9% to 4.4% with the increasing experience of the surgeon in performing PPH. The relatively high rate of postoperative bleeding implies that the vascular supply to the hemorrhoids is not interrupted by PPH as hypothesized. Instead, Aigner et al. demonstrated with anatomical dissections that neither PPH nor Doppler ligation completely interrupts the superior rectal artery branches, and of course there is still the vascular supply from below.

3. Bleeding rectal polyps and retained staples causing bleeding
Bleeding polyps represent a granulomatous foreign body reaction to retained staples, and have been shown to occur in 11% of patients after PPH. This is a late complication occurring between postoperative week 6 and 16. Retained staples, besides causing bleeding, may also be a cause of chronic pain. Both bleeding and pain may respond to transanal staple removal, which is one of the most frequent reinterventions after PPH.

4. Skin tags, thrombosed external piles, fecal impaction, proctitis
Skin tags are more frequent after stapled hemorrhoidectomy. Thrombosis is unlikely after excisional hemorrhoidectomy but may occur in up to 5.9% of cases after PPH if an external component and prolapse are present. Fecal impaction requiring enema and constipation can occur. Chronic proctitis, possibly secondary to ischemia, has been reported.

5. Fissures
They occur rarely (0.2% according to Slawik et al. and may be due to the trauma of a forceful insertion of the stapler into a tight anus in young males. There was no discernible difference between PPH and manual hemorrhoidectomy in the incidence of postoperative anal fissure in recent reviews.

6. Anal stenosis
Although no meta-analysis showed differences in postoperative anal stenosis, a prospective randomized trial of PPH vs. Ferguson hemorrhoidectomy reported anal strictures in 2.6% vs. 0%, respectively. Incidence of postoperative stenosis was 8.8% and 1.6% in two retrospective series. Most of the cases responded to anal dilatation while surgery was required in 1.4% of patients. Most of the strictures occurred in the early postoperative period in a series published by surgeons who perform the purse-string lower than usual, excising most of the pile and therefore taking more risks in terms of potential fibrosis of the upper anal canal. Dilatation after stricture was reported to result in a perforation causing retropneumoperitoneum.

7. Rectal stricture
It is possibly related to pre-PPH sclerosing injection and accompained by severe anal pain, occurred in 2.5% of patients in a Chinese series. Stricture may also respond to gentle dilatation with a Foley catheter under tension.

8. Local abscess or fistula
It occurs with a frequency of 0%–3%. Reporting on a series of patients who had surgery for co-existing anal lesions at the time of PPH Ng et al. describe a severe perianal abscess requiring reintervention following PPH and fistulectomy. A curious case of anal sepsis secondary to the passage of a chicken bone through a dehisced staple line has recently been reported.

9. Rectovaginal fistula
Fistula is more likely to be due to local ischemia rather than to a direct trauma and usually becomes

evident days after the operation. A careful vaginal inspection during the procedure helps to minimize the risk of such harmful event, which may require a reoperation. A simple trick aimed at preventing a lesion to the vagina, and also to the prolapsed pouch of Douglas, is to inject saline under the anterior aspect of the rectum, below the mucosal layer; this increases the distance with the vagina and reduces the risk of taking a bite of vagina while placing the purse string and firing the gun.

10. Complete rectal obliteration
It may be due to erroneous placement of a purse string or to firing the stapler outside the purse string in a blind pocket from redundant rectal mucosa. A careful deep digital exploration of the rectum after the procedure should alert the surgeon to the occurrence of this complication, which may require either fluoroscopic insertion of a guidewire and subsequent dilatation or transanal release of the strictured area and subsequent refashioning of the anastomosis.

11. **Rectal pocket**
A partial slippage of the purse string may cause a pathological pocket in the lower rectum, resembling a diverticulum or an intramural fistula. This may lead to an intermittent collection of fecalith with subsequent inflammation and local sepsis mimicking a perirectal or perianal abscess and requiring a lay-open of the pocket.

12. Rectal dysplasia or adenocarcinoma
This is a rare but possible event, due either to a misdiagnosed hemorrhoid-like cancer repositioned upward with the pexy or to the development of a new neoplasm arising on an internal polypoid pile, again lifted up after the stapled mucosectomy. This troublesome event may be prevented with a careful selection of the patients, i.e. excising the long-standing polypoid hemorrhoids or sending the specimen for the histology routinely.

13. Penile trauma after active anal intercourse
Two heterosexual patients had severe penile trauma with wide excision of penile skin and dramatic bleeding requiring emergency hospitalization after active anal intercourse with companions who had undergone PPH. The trauma was caused by retained staples. Anal intercourse may result in condom damage. The message from these reports is that the surgeon has to inform patients and their partners about this potential complication and that is better not to perform PPH in persons who practice receptive anal sex.

14. Tenesmus and fecal urgency
Tenesmus affected 50% of the patients who underwent PPH for fourth-degree hemorrhoids one year after surgery in a prospective randomized trial that compared stapled hemorrhoidopexy with manual hemorrhoidectomy. This rate dropped to 25% after six months in another study but was not reported as a relevant problem in a recent metaanalysis. In a non-randomized comparison between PPH and Milligan-Morgan procedure in the treatment of fourth-degree hemorrhoids, tenesmus was experienced in 32% of patients submitted to PPH but in none of those who underwent Milligan-Morgan procedure; the difference was statistically significant. In a prospective study at 28 months of follow-up, fecal urgency was still affecting a large proportion (40%) of patients, was disturbing or severe in 24% and significantly affected the patient's satisfaction more than any other symptom. The frequency of urgency was lower but still present (14%) after an 87-month median follow- up, more often than after conventional hemorrhoidectomy (8%). This is likely to be due to a reduced rectal capacity, as shown by De Nardi et al.

This complication can be prevented by avoiding PPH in patients with reduced rectal compliance or increased rectal sensation, assessed by anorectal physiology testing, and in patients with fourth-degree piles.

Treatment may consist of transanal electrostimulation or sensory biofeedback. In cases resistant to conservative treatment, transanal agrapphectomy, aimed at removing fibrous tissue and increasing rectal capacity, may also be considered.

15. Fecal incontinence
Hemorrhoids are factors of anal continence as there is atrophy of anal the cushions in patients with idiopathic incontinence. Therefore, the upper replacement instead of excision of the piles carried out by stapled hemorrhoidopexy should favor continence. It is a matter of fact that incontinence may

follow PPH, even if it is not frequent. It may be limited to loss of flatus, but a temporary incontinence to stool has been reported in 3.2% of cases after PPH for fourth-degree piles and a higher fecal leakage rate up to 31% may be recorded. Soiling was present in 10% of cases after one year and decreased to 7% after 7 years.

Preoperative anal manometry and anal US may help to detect patients with a less compliant rectum and weak sphincters, thus minimizing the risk of post-PPH incontinence. In case of soiling due to localized trauma of the internal sphincters, the use of bulking agents such as injectable silicone or carbon-coated microbeads, or the injection of autologous fat may be of some advantage and achieves good results in up to 80% of cases. Sphincter repair is rarely needed, and was carried only in two out of 65 reinterventions after PPH.

16. Retropneumoperitoneum and pneumomediastinum
These complications may be due either to filtration of air through the staple line to the extraperitoneal space (facilitated by a wide excision of the rectal mucosa with a too deep purse string involving the whole rectal wall) or to leakage of bacterial content leading to pelvic sepsis and requiring a diverting stoma. This complication may be low-symptomatic and require just conservative treatment with intravenous fluid and delayed oral intake, or may present with diffuse abdominal pain and high white blood cell count and respond to bowel rest and intravenous antibiotics. Retroperitoneal air has also been reported after colonoscopy, transanal endoscopic microsurgery and transanal full-thickness excision of rectal tumors.

17. Rectal perforation, pelvic sepsis, rectal hematoma causing intestinal obstruction and other life-threathening complications
Life threatening complications after PPH are usually associated with anastomotic leakage or pelvic sepsis. Their frequency was 0.08 and 0.09% in two large series. Anastomotic dehiscence after PPH, which may lead to pelvic sepsis in case of full-thickness rectal stapling, was reported in 3.2% of 654 patients.

18. Urinary retention
It is a common complication following hemorrhoidectomy and occurs in 10 to 50% of patients. The risk of urinary retention can be minimized by limiting intraoperative and perioperative IV fluids, and by providing adequate analgesia.

Complications of Gastric Surgery

Shaji Thomas

Gastric operations constitute an increasingly large proportion of the general surgical workload. Although the incidences of complicated peptic ulceration and gastric cancer have declined significantly over the past several decades, gastric operations for treatment of morbid obesity have undergone explosive growth.

Peptic ulceration

There has been a worldwide decline in the incidence of uncomplicated ulceration and the rate of hospitalization for complicated disease. Bleeding, perforation and obstruction are the three major complications of peptic ulcer requiring surgical intervention, with bleeding the most common.

Infection with the gram-negative bacterium, *Helicobacter pylori*, is very strongly linked to the development of peptic ulceration. This organism is present in as much as 30% to 50% of the population. Most infected individuals remain without symptoms; only 6% to 20% of colonized individuals develop peptic ulcer disease. Conversely, *H pylori* is present in >90% of patients with ulcer disease.

Hemorrhage
NSAID use is an important risk factor for ulcer hemorrhage, and NSAIDs significantly increase the risk of bleeding in *H pylori* infected individuals. Ingestion of NSAIDs is associated with a twofold increase

in risk of bleeding in patients who are infected with *H pylori* relative to patients who are *H pylori* negative. Only 10% of patients with bleeding ulcers are both *H pylori* negative and without a history of NSAID exposure.

Advanced age (>60 years), concurrent illness, patients presenting with shock, and those with recurrent bleeding are at increased risk of death and should be treated in an intensive care unit.

Upper gastrointestinal endoscopy is the preferred diagnostic modality for upper GI hemorrhage. It can define the nature and site of the bleeding lesion, predicts risk of recurrent bleeding, and when necessary, tissue biopsy can be obtained for histology and diagnosis of *H pylori.* Ulcers with adherent clot, nonbleeding visible vessel, or active hemorrhage are associated with a high rebleeding rate. Endoscopic therapy (thermal coagulation or injection of vessel sclerosants or vasoconstrictor agents) is effective in most patients (>80%). Almost all patients who rebleed after endoscopic therapy do so within 96 hours of the initial endoscopic procedure.

Surgical treatment of rebleeding should be considered for patients who are at highest risk for continued bleeding, including patients with large ulcers and large bleeding vessels, the elderly (>60), patients with active hemorrhage, and patients with hypotension.

Surgery for bleeding ulcer has two therapeutic goals; bleeding must be controlled, and ulcer recurrence must be minimized. Through a duodenotomy, the bleeding vessel at the base of the ulcer is visualized and ligated. Currently, the role of an additional antiulcer procedure at this stage is debatable, as all these patients are now subjected to *H pylori* eradication therapy postoperatively and discontinuation of NSAIDs. Emergency vagotomy and pyloroplasty done in the past had an incidence of dumping of 1% to 10%, recurrent bleeding rate of 17%, and a duodenal leak rate of 3%.

Perforation

In the majority of patients, perforation is the first manifestation of duodenal ulcer disease. Risk factors that predict operative mortality include age >65 years, concurrent medical comorbidity, preoperative shock, long-standing perforation (>48 hours).

Operative treatment (open or laparoscopic) of perforated duodenal ulcer has four goals: patient safety, peritoneal debridement, closure of perforation, and minimizing risk of ulcer recurrence. The perforation is usually closed with omental patching. Simple patch closure is followed by ulcer recurrence rate of 61% within 20 months. *H pylori* eradication following omental patching reduces ulcer recurrence to <5%.

Gastric cancer

Gastric cancer risk is increased in stomachs that contain polyps. Risk is related to polyp histology, size, and number. Hyperplastic gastric polyps are considered to have no neoplastic potential. In contrast, adenomatous polyps have a definite risk for development of malignancy. The risk is greatest for polyps >2 cm in diameter. Multiple adenomatous polyps further increase the risk of cancer. Long-term infestation with *H pylori* also appears to predispose to subsequent development of gastric carcinoma.

Fiberoptic endoscopy is the definitive diagnostic method, and gastric biopsy will differentiate benign from malignant ulcers. CT scan demonstrates infiltration of gastric wall by tumor, gastric ulceration, hepatic metastasis, and extragastric spread. It is however less specific with regard to invasion of adjacent organs and in assessing for lymphatic metastasis. Endoscopic ultrasound characterizes subepithelial lesions, assesses the depth of gastric wall penetration by gastric cancer, and perigastric lymph nodes can be reliably identified and biopsied.

Surgical resection is the only curative treatment. The surgical objectives in gastric cancer are to attempt cure in patients with localized tumor and to provide palliation that is both effective and safe for patients with advanced malignancy.

The most important complication of total gastrectomy is anastomotic leak at the esophago-jejunal anastomosis – heralded by unexplained tachycardia without fever or leukocytosis. Water-soluble contrast radiography will confirm the leak. Intraluminal suction decompression and peri-anastomotic

drainage may be used to create a controlled fistula with expectant fistula closure. Severe surrounding inflammation usually prohibits direct operative repair. Anastomotic leakage contributes substantially to the reported operative mortality of total gastrectomy.

Morbid obesity

A BMI >40 kg per m^2 defines morbid obesity. A BMI of 35 kg per m^2 maybe accepted as morbid obesity in the presence of obesity-related complications such as diabetes mellitus. Morbid obesity is associated with increased risk of hypertension, noninsulin-dependent diabetes mellitus, hypertrophic cardiomyopathy, dyslipidemia, pulmonary insufficiency, osteoarthritis, stroke, cholelithiasis, sleep apnea, several types of cancer, and premature mortality. Obesity also has psychological and psychosocial consequences, for example, obese people often experience prejudice, discrimination, and psychological abuse from coworkers, family members, friends, and strangers making it harder for them to maintain personal relationships. They are also at a higher risk for anxiety and depression.

Operative intervention is recommended for morbidly obese individuals (BMI >40 kg per m^2) on the basis that weight reduction by nonsurgical techniques was seldom achieved. However, before surgery, the patient must provide evidence of failure to lose weight under medical supervision, and the motivation and emotional reserve necessary to undergo the surgical procedure and subsequent lifestyle changes. Bariatric surgery maybe contraindicated for patients with high risk factors such as severe congestive heart failure or unstable angina, those unable to understand the surgical risks and postoperative maintenance requirements, those who are active substance abusers, those with significant psychopathology (such as psychosis), and those with under- or untreated depression.

Contemporary bariatric procedures all involve a degree of gastric restriction. This is augmented by malabsorption in the biliopancreatic diversion procedure. After bariatric surgery, a mean of 60% of excess weight is lost by 24 months after operation. There is some weight regain between 2 and 5 years and stability thereafter. One study defined success as a loss of more than 50% of excess body weight and failure as loss of less than 30% of excess body weight at one year after surgery.

Intraoperative complications: Pressure sores and neural injuries (ulnar nerve and lateral femoral cutaneous nerve) are more common. Nerve injuries are usually caused by malpositioning or stretch and are neuropraxic and reversible.

Postoperative complications: Overall complication rates range from 20% to 40%. The most frequent postoperative complications include deep vein thrombosis (DVT), pulmonary embolism, anastomotic leakage, and wound infection. Late complications include stomal stenosis, staple line dehiscence, and marginal ulceration. Micronutrient deficiencies have also been reported.

Complications after gastric surgery

1. Deep venous thrombosis

Overall, the most common cause of death postoperatively is pulmonary embolism. DVT occurs in about 2% of these patients. Immobility, venous stasis, and effects of pneumoperitoneum may contribute to thrombus formation. Doppler examination is the preferred initial diagnostic test. Sequential compression stockings and injection of subcutaneous heparin or low molecular weight heparin are recommended for DVT prophylaxis. Physicians often recommend early and frequent ambulation.

2. Anastomotic dehiscence

Anastomotic dehiscence or suture line leak occurs in about 1% to 3% of patients undergoing bariatric surgery. The diagnosis of postoperative peritonitis is more difficult in morbidly obese patients. Tachycardia, worsening abdominal or back pain, and hiccups may be the only signs. They may also have nausea, vomiting, fever, hypotension, and oliguria. Concern mandates radiological investigation with a water soluble contrast agent. If a leak is confirmed at laparotomy, the defect should be closed if feasible and the upper abdomen should be externally drained. A gastrostomy tube should be placed in the distal, excluded stomach.

3. Postoperative hemorrhage

Unrecognized injury to the spleen is the most common cause of postoperative hemorrhage after operations on the stomach or duodenum. Splenic hemorrhage occurs as a result of capsular injury

from traction, inappropriately placed retractors, or failure to properly ligate short gastric vessels. Inadvertent splenic injury during upper abdominal surgery is among the most common indications for splenectomy. Splenectomy increases the incidence of hypovolemia, pancreatic fistula, pancreatitis, and septic complications including subphrenic abscess.

Intraluminal hemorrhage most commonly represents suture line bleeding. Gastric lavage followed by endoscopic hemostasis is usually successful. Uncontrolled hemorrhage is an indication for reoperation.

4. 'Dumping syndrome'

This is a common complication which refers to a group of symptoms (with both gastrointestinal and vasomotor symptoms) that can occur when calorically dense carbohydrates are ingested and when the stomach 'rapidly and without regulation empties its contents into the small intestine' – after vagotomy and either resection or division of the pyloric sphincter.

Symptoms, which can arise 15 minutes to two hours after eating and generally last about 30 minutes, may include tachycardia, dizziness, sweating, nausea, vomiting, bloating, abdominal cramping, and diarrhea. Early dumping symptoms occur within 1 hour of a meal and include nausea, epigastric discomfort, and palpitations. Severely symptomatic patients may also have dizziness or syncope. Late dumping symptoms follow a meal by 1 to 3 hours and may include reactive hypoglycemia.

Although 5% to 10% of patients experience mild dumping symptoms in the early postoperative period, minor dietary alterations and the passage of time bring improvement in approximately 60%. The somatostatin analogue octreotide has been reported to improve dumping symptoms when 50 to 100 µg is administered subcutaneously prior to a meal. The beneficial effects are due to pressor effects of the compound on splanchnic vessels and inhibition of the release of vasoactive peptides from the gut. Octreotide also decreases peak plasma insulin levels and slows intestinal transit.

5. Cancer in the gastric remnant

Gastric cancer is more likely to develop in individuals who have undergone previous partial gastrectomy. The clearest risk factor is the time interval following surgery. A decreased risk of gastric cancer has been observed during the first 15 years after gastrectomy. From 15 to 20 years after gastric resection for ulcer disease, patients have a relative risk for gastric cancer that is three to five times that of the age-matched and sex-matched general population.

6. Gastric outlet obstruction and small bowel obstruction

Gastric outlet obstruction and small bowel obstruction occur in 3% to 5% of cases after gastric resection. The major cause of anastomotic obstruction in the early postoperative period is inflammation adjacent to the anastomosis, secondary to subclinical suture line leakage or ischemia. Chronic gastric outlet obstruction is often the result of perianastomotic ulceration with resultant cicatrization. Pain is usually not a prominent symptom. Recurrent vomiting or persistently elevated nasogastric tube output suggests the diagnosis. Fibreoptic endoscopy evaluates the anastomotic patency. In a Billroth II anastomosis, patency of each limb should be evaluated. An open anastomosis favors delay in reoperation and support of nutritional needs with parenteral alimentation.

When a gastrojejunostomy is performed in a retrocolic position, obstruction may be due to occlusion of the anastomosis by the transverse mesocolon. Volvulus of the proximal or distal limbs of the gastrojejunostomy is possible following Billroth II reconstruction, more commonly when the anastomosis is antecolic.

The afferent loop syndrome is a condition caused by partial obstruction of the proximal limb of a gastrojejunostomy due to kinking or torsion of the anastomosis, obstruction by the transverse mesocolon, internal hernia, or recurrent ulceration. This results in intermittent dilatation of the duodenum and proximal jejunum, with periodic release of pancreatic and biliary secretion into the stomach. Afferent loop obstruction occurring in the immediate postoperative period causes severe and unrelenting epigastric pain. Acute afferent loop obstruction is a surgical emergency as it can cause duodenal stump leakage. The dilated loop can be visualized on a CT scan; the obstructed limb will not contain orally ingested contrast. This condition requires urgent reoperation because of the possibility of perforation.

Jejunogastric intussusception is an unusual cause of gastric outlet obstruction, with the efferent limb being the source in more than three-fourth of patients. Urgent endoscopy reveals a friable, bluish mass originating from the orifice of the efferent limb. Abdominal CT scan reveals a mass within the stomach with a layered, onion skin-like appearance. Urgent operative reduction is indicated due to the potential for ischemic necrosis of the intussusception.

7. Acute gastric dilatation

Acute gastric distension of the bypassed distal stomach can occur as a result of postoperative peritonitis or as a mechanical consequence of an obstructed enteroenterostomy. Continuous abdominal pain, distension, and hiccups are frequently associated signs. Plain x-rays or CT demonstrate massive gastric dilatation, often with an air-fluid level. Acute gastric distention must be treated emergently because of the potential for ischemic necrosis of the stomach. Percutaneous or operative gastrostomy decompression is therapeutic.

8. Postsurgical gastroparesis

This is a chronic complication of gastric surgery characterized by disruption of the normal mechanisms of gastric motility. Affected patients will have postprandial pain, nausea, and vomiting, along with difficulty in maintaining adequate oral nutrition. The pathogenesis of this condition is unknown. Lack of vagal tone, abnormalities of neuromuscular coordination, disordered smooth muscle function, and motor abnormalities of the Roux-en-Y limb have been postulated.

The diagnosis requires absence of anatomic obstruction, including anastomotic stricture and efferent limb obstruction. Fibreoptic endoscopy of the gastric remnant and contrast studies of the small intestine will exclude distal obstruction or generalized intestinal hypomotility. Radionuclide solid phase gastric emptying studies are used to evaluate gastric function and to assess effectiveness of medical therapy.

Endocrine disturbances like hypothyroidism and diabetes mellitus, diseases like amyloidosis, scleroderma, muscular dystrophy, myasthenia gravis, and psoriasis, and medications like narcotics and anticholinergics can alter gastric emptying.

Patients should receive a prolonged trial of prokinetic drug therapy.

9. Duodenal fistula

Complication of gastric resection when duodenum is closed and gastrojejunal reconstruction performed. This is a particularly morbid condition because of the high fluid volume lost and because of the escape of pancreatic and biliary secretions into the peritoneal cavity. Attempts at immediate operative closure are futile. Initial management is concerned with treatment of sepsis, control of intraperitoneal leakage, and skin protection at any site of external drainage. Parenteral alimentation is necessary to maintain positive nitrogen balance.

When distal obstruction exists in the afferent jejunal limb, spontaneous fistula closure will not occur. If spontaneous closure does not occur within 6 weeks, operative repair is justified.

10. Avulsion of the Sphincter of Oddi

Operative injury to the ampulla of Vater is a serious but rare event during gastric resection. This injury occurs during dissection between the duodenum and pancreas prior to duodenal transection. Intraoperatively this can be recognized by the sudden appearance of bile in the operative field. Postoperatively, the injury causes collection of bile and pancreatic secretions in the subhepatic space. If this injury is recognized intraoperatively, the duodenal stump may be mobilized further and brought over the ampulla. The ampulla or the individual bile and pancreatic ducts may then be reimplanted. A Roux-en-Y limb of jejunum may also be created for this purpose. When discovered postoperatively, inflammatory changes make ductal reimplantation impractical and pancreaticoduodenectomy becomes necessary.

11. Incisional hernia

Postoperative incisional hernias occur in approximately 20% of cases of open bariatric surgery. Port site incisional hernias have been reported in upto 0.5% of patients after laparoscopic gastric bypass, representing the clearest advantage of the laparoscopic approach.

12. Cholelithiasis

Rapid weight loss following surgery is associated with an increased risk of cholelithiasis. Half of patients following bariatric surgery will demonstrate gallbladder sludge; one-third will develop symptomatic gallstones. The use of prophylactic ursodiol for 6 months following gastric bypass has reduced the incidence of symptomatic gallstones to 2%. Many surgeons have used the high incidence of postoperative cholelithiasis to justify prophylactic cholecystectomy at the time of gastric bypass. No controlled trial exists to support or refute this practice, and this is no longer recommended.

13. Stomal complications

The gastrojejunal anastomosis that drains the proximal gastric pouch in gastric bypass is intentionally small at 1 cm. Larger stomas do not create enough restriction of food passage and are not associated with adequate weight loss. As a consequence, stomal stenosis is relatively common, occurring in about 12% of cases. Affected patients develop early satiety, recurrent vomiting, and upper abdominal pain. Thiamine deficiency has been linked to persistent vomiting, with disturbances in vision and gait. Stomal stenosis may also cause symptoms of gastroesophageal reflux.

Upper endoscopy is the preferred means of investigation; most patients will respond to endoscopic dilatation.

Stomal ulceration may also cause stomal stenosis. The rate of gastrojejunal stomal ulcer approximates 10%. The etiology of stomal ulceration is often multifactorial, including acid secretion by parietal cells in the proximal pouch, ischemia of the jejunal limb, and NSAID use. Failure to heal with proton pump inhibitors and elimination of NSAIDs suggests jejunal ischemia; mucosal biopsies are confirmatory. Prolonged ulceration causes mechanical obstruction because of chronic cicatrization.

Staple line disruption is a complication of gastric bypass techniques in which the stomach is not divided. This complication is suggested by recurrent weight gain after weight loss stabilization. Correction requires reoperation to restaple and divide the stomach. Staple line disruption occurs in 1% of patients.

Nutrient deficiencies are anticipated after Roux-en-Y gastric bypass because the distal stomach and duodenum are bypassed. Defective absorption of vitamin B_{12}, folate, iron and calcium are sufficiently common to warrant routine postoperative supplementation. Biliopancreatic diversion worsens micronutrient deficiencies because of the more severe anatomic rearrangement. Steatorrhoea is universal and high dose calcium supplementation and monthly intramuscular vitamin D are required to prevent metabolic bone disease. Protein malnutrition is the most severe complication of biliopancreatic diversion.

14. Death

Overall, death occurs in 0.15% to 0.64% of patients undergoing bariatric surgery. The common causes of death are pulmonary embolism (15% to 32%), cardiac complications (13% to 18%), sepsis (18%), anastomotic leak (15%), gastrointestinal bleeding or hemorrhage (8%), bypass obstruction (5%), and small bowel obstruction (3%).

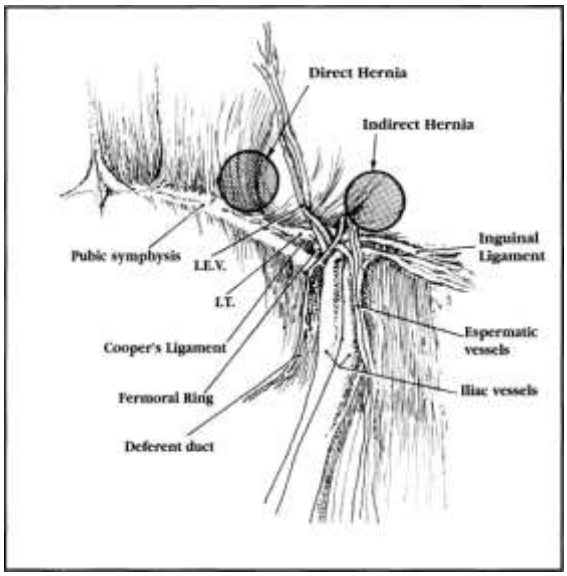
Complications of laparoscopic hernia repair

Arun Prasad

The rate of serious complications associated specifically with a laparoscopic approach is overall low. Up to half of complications occur at the time of abdominal access for camera or port placement [1]. Complications can also arise from abdominal insufflation, tissue dissection, and hemostasis [2]. Conversion to an open procedure may be needed to manage complications that have been identified intraoperatively, while others may not be recognized until the postoperative period. Severe complications such as vascular injury and bowel perforation can be catastrophic and are the main cause of procedure-specific morbidity and mortality related to laparoscopic surgery. Complications related to initial abdominal access occur in less than 1 percent of patients [3]. Once abdominal access is established, complications during the course of the procedure are similarly rare.

The increased acceptance of inguinal hernia repair by a laparoscopic approach has led to many confused reports on technique, results, and complications related to this procedure [4]. With the addition of inguinal hernioplasty, a new list of specific complications involving this procedure has appeared. Many of these complications are directly related to lack of thorough knowledge of surgical anatomy (Figure 1), or to improper technique [5].

MacFayden [6], presented a report on 359 hernias submitted to surgery in 328 patients using the TAPP technique. Postoperative complications included hematomas (11 cases), pain in the thigh (eight cases), scrotal emphysema (eight cases), and urinary retention (seven cases), with a total 10.3% morbidity. This result was to be repeated in subsequent studies, leading us to think that the learning curve would always present us with these rates in early analyses.



Phillips [7] published a multicentric study with 3,229 laparoscopic herniorrhaphies in 2,559 patients, revealing 336 (10%) complications and two deaths (0.06%). The TAPP technique (1,944 hernias) had 19 recurrences (1%) and 141 (7%) complications, similar to the rates in our cases, which had 0.9% recurrences and 8.2% complications. Using the same approach, Geis3 reported 0.6% recurrences.

In studies by MacFayden and Phillips, laparoscopic inguinal herniorrhaphy with intraperitoneal mesh presented 7% to 14% postoperative complications. However, early recurrences occurred in 2% to 3% of the cases. The fully extraperitoneal technique had 7.7% to 10% complications, with a low recurrence rate. Due to the use of mesh in laparoscopic herniorrhaphies, all recurrences involve technical errors, folds in the mesh, non-coverage of the defect or flaws in fixation. Early recurrences do not appear only after laparoscopic corrections.

Although it is not considered a complication, the recurrence of inguinal hernia is a form of morbidity and should be considered as such. The recurrence of laparoscopic hernia repair in various series, using the preperitoneal transabdominal technique (TAPP), appears to result from inadequate surgical technique. The inadequate fixation of mesh, inadequate size of the mesh (small) and a flaw in covering unidentified hernial defects (hernias which had never been repaired) are the main reasons for early recurrence of hernia. It is accepted that the causes of late recurrence of hernia could be stress on the tissues and the intrinsic weakness of the collagen. Since the laparoscopic technique uses synthetic material, and follows the principles of hernioplasty without tension, it is to be expected that the laparoscopic technique will not cause a significant number of late recurrences.

The rate of infection in the skin orifice is less than 1%, according to several studies. Treatment is simple, consisting of drainage and dressings. Antibiotics are used only when there are systemic repercussions.

Major bleeding during inguinal hernia repair is not a usual complication, but can occur due to injury of the inferior epigastric vessels during surgical dissection or the fixation of the mesh with staples. Bleeding must be controlled with sutures or clips; electrocautery is usually not effective. During surgical dissection, the peritoneum should be incised in a region which lies distant from the epigastric vessels and, using traction, it should be incised the full length required to correct the hernia. Traction and preperitoneal dissection caused by pneumoperitoneum are important in preventing injury to the inferior epigastric artery. Blunt dissection with a gauze cylinder is very useful to separate the epigastric vessels from the peritoneal flap.

The spermatic vessels may suffer injury when dissecting the spermatic cord, especially in the technique using split mesh for repair. In these cases the cord must be dissected and subsequently repaired. Special care must be taken in handling the spermatic cord. It should not undergo excessive traction, and hemostasis of bleeding cord vessels should be accurately secured as many collections

and hematomas during the postoperative period can be avoided. Equally, in indirect hernias, when separating the hernial sac, it is extremely important to perform strict hemostasis of the dissected area during its release.

Vascular injury to the iliac vessels can be severe and generally occurs because of staples placed in the region of the so-called “Triangle of Doom.” This triangle is limited medially by the deferent duct and laterally by the spermatic vessels in the male and round ligament in the female.

Ischemic orchitis is an important, but relatively rare, complication that may occur after hernia repair. Most cases occur after repair of large indirect hernias and are related to the extent of surgical trauma in dissection of the hernial sac. Testicular atrophy appears less frequently when there is no dissection of large segments of the vascular elements of the spermatic cord.

Inguinal Seromas occur more often in fully extraperitoneal repairs, presumably because the liquid cannot drain to the peritoneal cavity.

Patients who undergo laparoscopic herniorrhaphy have 1.6% incidence of neuralgias, a rate similar to that of open approaches. In laparoscopic inguinal surgery, the iliopubic tract is an important anatomic feature. Lateral to the spermatic vessels, and immediately below the fibers of the iliopubic tract, are the genital and femoral branches of the genitofemoral nerve, the femoral nerve and the lateral femoral cutaneous nerve. Consequently, clips placed below the iliopubic tract and lateral to the femoral vessels may cause temporary or permanent neuralgias, involving one or more of the nerve branches mentioned above.

It should be recalled that, even in laparoscopic surgery, the iliohypogastric and ilioinguinal nerves may be injured if the clips are applied too deep in the muscles of the anterior abdominal wall.

Bowel injury may occur in various laparoscopic situations, especially when the technique used is transabdominal (TAPP, IPOM). It may occur at initial puncture, particularly in an abdomen which has been submitted to previous surgery, or in an attempt to free peritoneal adhesions. A major problem can be incarcerated hernias, which may require opening the hernial ring or even conversion to a conventional procedure. In our experience, the installation of a pneumoperitoneum helps reduce incarcerated hernias. In strangulated hernias, the laparoscopic approach can accurately evaluate the viability of the bowel loop involved, which is not always possible in the conventional approach. A direct inguinal hernia sometimes contains a portion of the urinary bladder, which may be injured during dissection or stapling. This injury does not cause significant morbidity if immediately corrected with primary suture in association with decompression of the urinary bladder with a Foley catheter.
Special attention should be dedicated to the puncture sites. After removal of the cannulas, one should look for possible bleeding, as cases of injury to the epigastric artery with hypovolemic shock have been described. The aponeurosis at the puncture sites, especially at the orifices of the 10 mm and 12 mm trocars, should be closed to prevent local herniation.

After completing the procedure, it is useful to evacuate the pneumoperitoneum under direct viewing. The peritoneum is pressed against the abdominal wall internally with an instrument, while the surgeon presses externally.

Scrotal ecchymosis and inguinal hematoma caused by small bleeding vessels as a result of the surgical procedure are some of the most frequent complications following inguinal hernia repair. These lesions may be lessened or prevented using an elastic support for 3-4 weeks postoperatively.

Testicular edema normally occurs when the closure of the internal inguinal ring is excessively tight around the spermatic cord. It is rarely the result of venous or lymphatic injury. Treatment is simple, with suspension of scrotal sac and restricted physical activity. Anti-inflammatory medication may be used.

Laparoscopic herniorrhaphy is a feasible option, with low morbidity and mortality, less postoperative pain and a rapid return to normal activities.

However like any surgical procedure, complications are known and bound to happen some time or the other. Prevention, early diagnosis and prompt action would remain the 3 corner stones of management of complications following laparoscopic hernia repair.

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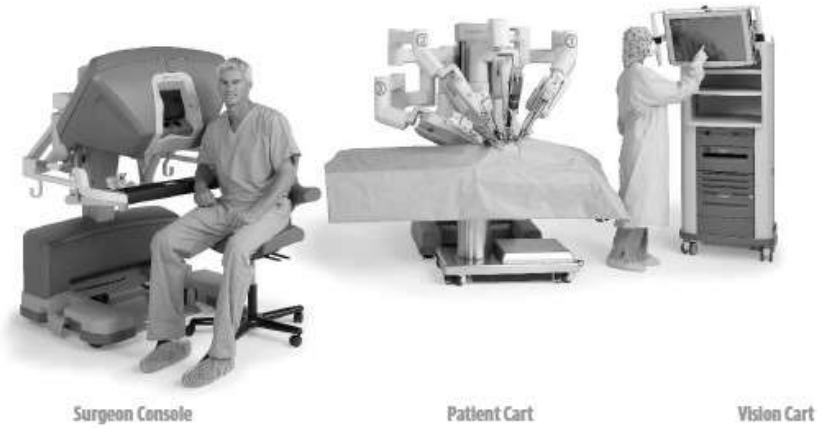
Preparing the Robotic System for Surgery

Manav Suryavanshi

System Overview

The *da Vinci Si* system consists of three components: the Surgeon Console, the Patient Cart and the Vision Cart.



Surgeon Console

The Surgeon Console is the control center where the surgeon sits outside the sterile field, using eyes, hands and feet to control a 3D endoscope and *Endowristed* instruments, by means of two master controllers and foot pedals.

Patient Cart

The Patient Cart is the operative component of the *da Vinci Si* system, and it supports the instrument arms and camera arm. The Patient Cart operator works in the sterile field, assisting the Surgeon Console operator by exchanging instruments and endoscopes, and by performing other patient-side activities.

Vision Cart

The vision cart houses the system's central processing and vision equipment. It includes a touchscreen monitor and provides shelves for ancillary equipment such as electrical surgical units and insufflators. It is operated by a nonsterile person during surgery.

Preparing the Patient Cart for Draping

The patient cart arms are prepared for draping by moving each arm's insertion axis to a vertical position (90º). Draping makes the Patient Cart arms sterile and suitable for surgery.

Draping Guidelines

For speed, sterility and safety, a two-person team should do draping: a scrub nurse or surgical assistant and a circulating nurse who can handle non-sterile components.

- Drape the arms systematically, moving from left to right or right to left.
- First drape instrument arm 3 (if it will be used).
- Using the **clutch buttons**, the circulating nurse should move each straightened arm to provide room to maneuver around the arm.
- Once an arm is draped, the scrub nurse should move the draped arm away from the undraped arms and prepare to drape the next arm.

To drape the *da Vinci Si,* you need two or three (in case using the fourth arm) instrument arm drapes, a camera arm drape, and a camera head drape.

Instrument Arm Draping Procedure

1. **Circulating Nurse:** Deliver the instrument arm drape to the scrub nurse in sterile fashion, with the instrument arm sterile adapter facing the ceiling.
2. **Scrub Nurse:** Unfold the drape on a sterile table.

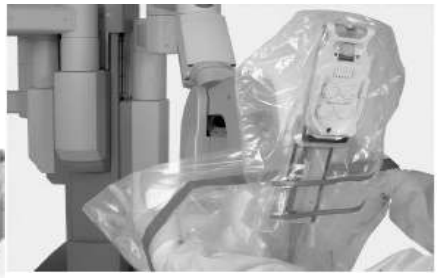
3**.** Tent the opening of the drape and grip the outside with your finger and thumb. Hold the top of the drape with the other hand. Lower the drape over the instrument arm insertion axis.

4**.** Insert the base of the sterile adapter into the black molded piece into which it fits. Using both thumbs, push the sterile adapter into the instrument arm until it clicks into place. The **wheels on the sterile adapter will spin**, and you will hear three beeps, indicating that the system recognizes the sterile adapter.

5. Remove the two tear-aways on the front of the drape.

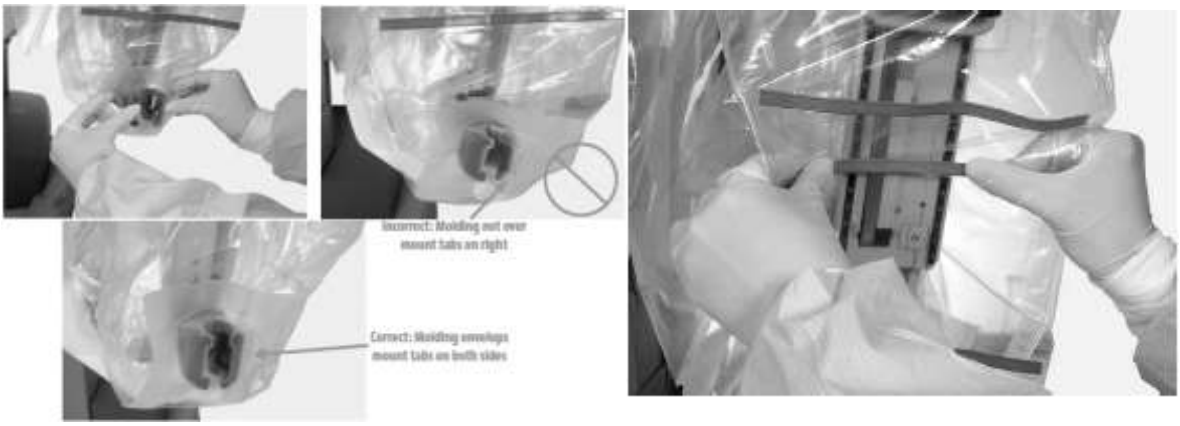
6. Using the cuff of the drape, move it back along the instrument arm toward the Patient Cart tower

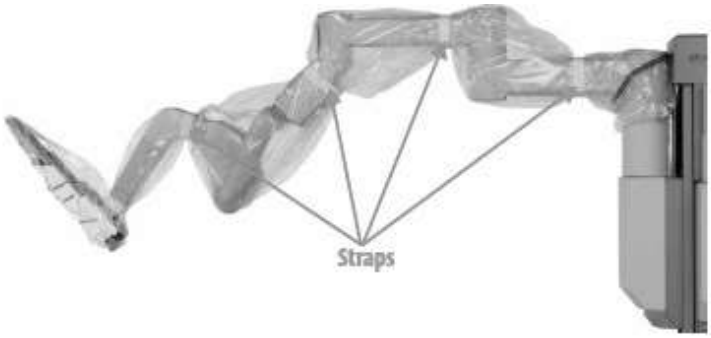
7. Seat the cannula mount molding. Make sure the molding snaps over the cannula mount



8. Wrap all white drape straps snugly around the instrument arm, and attach each strap to itself. The arm should move without tearing the drapes or straps, adequate redundancy in drapes should be maintained.

9. Bend the blue flex-strips to create a clear instrument insertion path along the axis of the instrument arm.

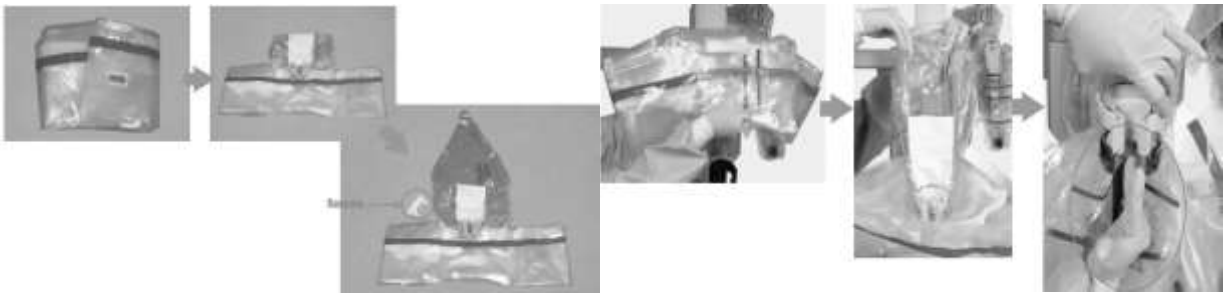




Camera Arm Draping Procedure
Before you begin draping the camera arm, the sterile person should move the draped instrument arms away from the camera arm, to provide plenty of room to walk between the arms.

1.**Circulating Nurse:** Deliver the camera arm drape to the scrub nurse in sterile fashioning the arrow-side facing up.

2.**Scrub Nurse:** Unfold the drape on a sterile table and remove the white retainer from the sterile adapter (Fig. 10).
3.Insert one hand into the bottom opening of the drape and hold the top of the drape with the other hand. Lower the drape over the insertion axis and then lift the top of the drape over the top of the arm's insertion axis.



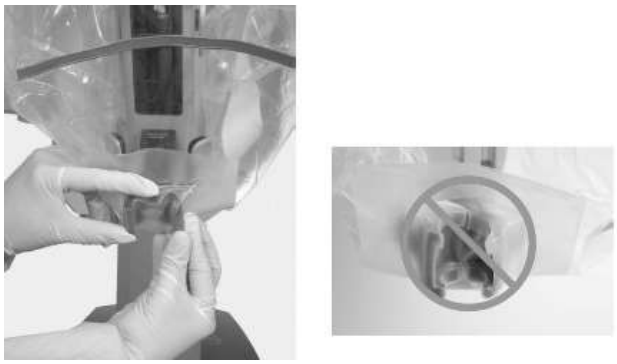
4. Now install the camera arm sterile adapter into the carriage on the camera arm. Using the side of one hand as shown above, make a trough in the drape through the carriage to create room for the endoscope to pass through. Then firmly push into place the camera arm sterile adapter (Fig. 11).

5.Using the cuff of the drape, move the drape down along the camera arm setup joint to the center column of the Patient Cart (Fig. 12).

Fig. 12: Extend Drape to the Center Column and Secure

6.Use your hands inside the drape cuff to engage the opposing Velcro strips near the center column.

7.Seat the cannula mount molding. Make sure the molding snaps over the cannula mount (Fig. 13).



8.Wrap the white drape straps snugly all the way around the camera arm and tape each strap's end to itself.

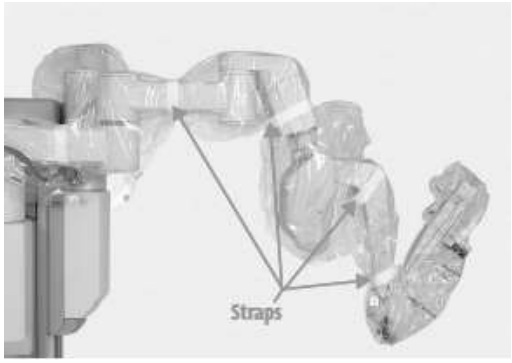


Fig. 14: Camera Arm Drape Secured with Straps

8. Bend the Blue flexi-strips to create a clear path for the endoscope along the arm's insertion axis and to ensure camera arm drape does not stretch or tear during system operation (Fig. 15).

9. ***Fig. 15: Bend the Blue Flex-Strips Around the Insertion Axis***

Camera Head Draping Procedure
Since the Vision Cart and cables are not sterile, a non-sterile person (circulating nurse) must assist a sterile person (scrub nurse) with draping and connecting the camera head. (The camera head itself is not sterile and must not be autoclaved.) To drape the camera head:

1.**Circulating nurse:** Deliver the camera drape to the scrub nurse in sterile fashion.

2.**Scrub nurse:** Unfold the drape. Then insert a hand into the open end of the drape, and grab the camera head sterile adapter firmly.

Fig. 16: ***Attaching Camera Head to Sterile Adapter***

3.**Circulating nurse:** Attach the camera head to the camera head sterile adapter. You must align the pins in the sterile adapter with the channels in the camera head, push down and turn to lock it in place.

4.**Scrub nurse:** Invert the drape over the camera head.

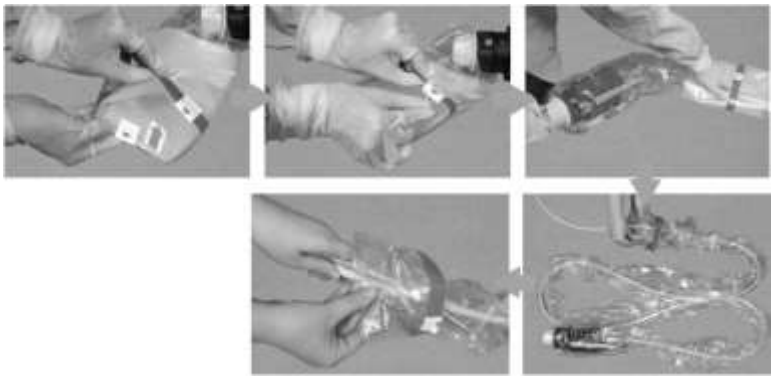


Fig. 17: ***Invert Drape over Camera Head, Pull Along Cables***

5. **Circulating nurse:** Pull the drape along the cables.

Endoscopes

Install Endoscope on Camera Head

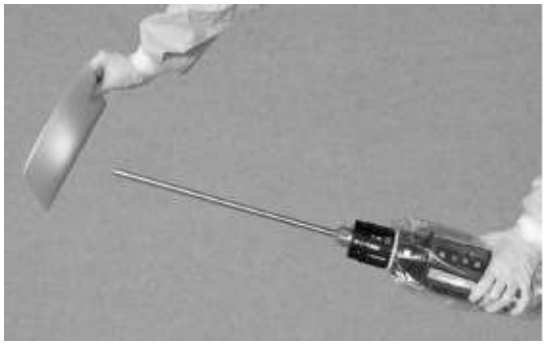
- Hold the endoscope and camera head with attached sterile adapter firmly in each hand—avoid dropping either part. If you are installing an angled endoscope, the orientation with which you install it determines whether the scope is 30 degrees up or down. (The system automatically detects and displays it, whichever way it is installed.)
- Place the endoscope base over the sterile adapter, turning the scope as necessary until the scope slides down over the camera head sterile adapter.
- Push down the scope until it bottoms and turn to lock it in place.

Steps to Setup the Vision System
There are two basic steps to setup the vision system:

- Set the white balance
- Calibrate the endoscope/camera assembly

Setting the White Balance

1. Turn on the lamp by pressing the **Lamp On/Off** button on the camera head or illuminator front panel.
2. Point the endoscope at a white object so the object covers the entire field of view. You must white balance the camera at the start of each procedure and any time a camera head or endoscope is changed. White balance sets a white color benchmark for the vision system.
3. Press and hold for 1 second the **Vision Setup** button on the camera head. (You can also use the White Balance button on the touchscreen or touchpad.) A message will appear on the screen indicating when white balance is complete.



Calibrating the Endoscope Assembly

- The *da Vinci Si* system automatically detects the scope angle, which is necessary to perform calibration. If the system does not detect the scope angle, the touchscreen enables you to manually select the scope angle.
- Perform calibration at the start of each procedure for all endoscopes and angles you expect to use with the current camera head and its sterile adapter. The system saves the last calibration for every combination of endoscope, angle and camera head, so if you follow this recommendation, it enables you to change angles (and scopes when using both a 0 degree and 30 degree up/down scope) during a procedure without having to recalibrate.

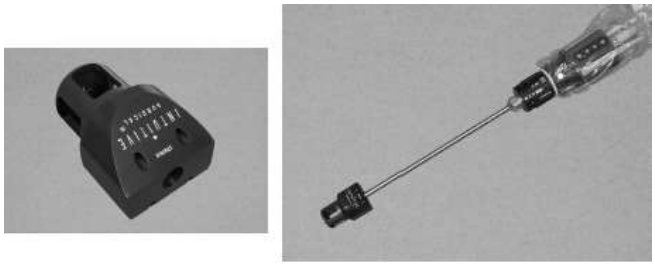
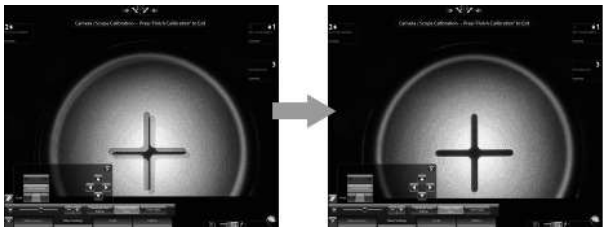


Fig. 19: Endoscope with Alignment Target

1. Insert the endoscope tip fully inside the endoscope alignment target, using the proper hole and orientation, which depends on the tip angle, so that the target crosshairs are visible and run vertically and horizontally on the touchscreen. Use the **Focus In** and **Out** buttons on the camera head to focus the image.



2. Touch the arrows on the touchscreen to move the green crosshairs until aligned with the magenta crosshairs.

Fig. 20: Aligning Crosshairs

3. Touch **Finish Calibration** on the touchscreen or touchpad to save the calibration setting and exit calibration mode.

Docking

Docking is the process of moving the Patient Cart up to the OR table and connecting the Patient Cart arms to the patient.

Patient Cart Positioning
Move the patient cart towards the patient. Make sure the camera arm is sufficiently away from the patient cart tower to facilitate adequate range of motion for the patient cart arms. This is known as setting the **"sweet spot".**

To set the "sweet spot" move the camera arm so that the blue arrow lies between the limits of blue bar located in the middle of the camera arm setup joint. (left or right side)

Fig. 21: Aligning the Sweet Spot

The Patient Cart should approach the patient with the tower of the Patient Cart lined up in a straight line with the **camera cannula** and the target anatomy
Position the Patient Cart so the camera arm cannula mount is just above the camera cannula. Use the camera arm clutch to bring the cannula mount to the cannula and dock it closing the snap locks.
Use the instrument arm port clutch button to bring the instrument arm cannula mount to the cannula and dock it closing the snap locks.

Install the camera and instruments in the robotic arms and the robotic system is prepared and ready to be used.

References

- **DaVinci Manual**
- **DaVinci Online Community**

Management of a Burns Patient - An Overview

Prabhat Shrivastava

Injuries that result from direct contact or exposure to any thermal, chemical, electrical, or radiation source are termed as 'burns'. Pathologically, a burn injury results in the coagulative necrosis of the involved tissues. An extensive burn injury carries a high morbidity and mortality. The management poses a major challenge and requires a dedicated multidisciplinary team approach.

On-site management (Pre-hospital care)

The first aid, provided promptly at the scene of the accident, in an effective & systematic manner reduces the extent, limits the depth of burns & minimizes the morbidity.

In *thermal burns*, rescuing the victim from burning premises takes precedence over putting out the fire. Flames should be doused with tap water, or smothered with a rug or a blanket. Goal is to bring down the skin temperature to normal as quickly as possible. Application of ice/ ice cold water is not recommended as it further reduces tissue perfusion & can rapidly cause hypothermia in small children. The hot metallic ornaments should be removed. The victim should be made to lie supine. Airway, breathing & circulation should be assessed & if there is no response, CPR should be started. Burnt area should to be covered with a clean dry sheet to prevent contamination, hypothermia and pain. IV infusion & endotracheal intubation are usually not required at the accident site. When inhalation injury is suspected, oxygen should be administered on way to the hospital.

Initial management of all *chemical burns* is the same irrespective of the agent. Clothing contaminated with chemicals should be immediately removed. Copious water irrigation should be done by keeping the affected area under running tap water to neutralize/flush away the noxious chemicals. Time should not be wasted in looking for the specific antidotes. In *electrical burns*, the current source should be switched off before removing the victim. If the supply cannot be cut, the rescuer should use a non-conducting material like wood to separate the victim from the electric source.

Any lotions/ colouring agents/ household remedies should not be applied over the burnt area as they make the formal assessment of the extent & depth of burn wound difficult. Moreover, removal of such substances might be difficult & painful to the patient.

Management in the Hospital / Burns Department

History of a burn injury gives valuable information about the nature & extent of the burn, depth of burn, likelihood of inhalation injury, and probability & location of any associated trauma. Brief history of previous medical conditions, medications, allergies etc. should also be taken from relatives/parents. Burn victim, like any other trauma victim should be *evaluated systematically* on arrival to the hospital emergency. A modified ATLS primary survey must be done followed by a quick secondary survey. After establishment of airway, ventilation & systemic perfusion, the next priority is diagnosis of any *associated life-threatening injuries*. Closed head injury, pneumothorax & other thoracic trauma, spinal injury, intra-abdominal injuries, pelvic & long bone fractures etc., should be ruled out. Intravenous access should be established with a large bore cannula, preferably through unburned skin & Ringer lactate infusion should be started.

The burn wound should then be assessed for its *extent* in relation to total body surface area & *depth,* which are required to formulate the plan of management (inpatient/outpatient treatment, referral to burn centre, estimation of initial fluid needs, surgical/conservative approach, prognosticate the relatives wrt survival, healing time, surgical interventions, scarring, morbidity, rehabilitation needs etc).

Estimation of extent of burn

Several formulae & charts have been devised to estimate the percentage of the TBSA burned. Lund & Browder's chart, although tedious to use is the most accurate method to assess the exact extent of burn for all age groups. Wallace's 'Rule of Nine' for adults and modified 'Rule of Nine' for children are also considered reasonably accurate. For all age groups, the surface area of patient's own palm (including fingers) is approx. 1 % of TBSA. It can be used to estimate relatively small & scattered burns.

Estimation of depth of burn

Depth of the burn is largely determined by temperature of the burning agent, its duration of contact and thickness of the skin. In a *partial thickness* burn, epidermis and only part of dermis is burned & healing occurs by spontaneous epithelialization form sweat glands, sebaceous glands & hair follicles which are located deep in the dermis. However, entire thickness of dermis with all its appendages is destroyed in a *full thickness* burn and this would require skin grafting. Based on the depth of the skin involved, the burn wound has also been graded into I, II, III and IV degree burn. First degree burns should not be included in TBSA burned for burn management.

Criteria for transfer to a burn centre

Minor burns (partial thickness burns <2% in infants, <5% in older children and <10% in adults) may be managed on OPD basis. All other burns need to be hospitalized. Following are the defined criteria for admission to a specialized burn centre:

1. Second degree burns >10% TBSA
2. Third degree burns
3. Burns involving face, hands, feet, genitalia, perineum and joints
4. Inhalation burns
5. Chemical burns
6. Electrical burns
7. Burns with associated trauma
8. Pre-existing disorders that could complicate management or prolong recovery
9. Hospitals without qualified personnel or equipment

Cases of suspected child abuse, parental inability to care for the child and non-availability of transport for follow-up visits should also be admitted to the hospital.

Tetanus prophylaxis is ensured by giving Inj. Tetanus Toxoid im to all patients. In non-immunized patients, 250 units of tetanus immunoglobulin are also given im for passive protection.

Respiratory support

Direct thermal damage to upper respiratory tract rapidly leads to upper airway oedema. Additionally, carbon monoxide poisoning and lung parenchymal damage due to inhalation of smoke and toxic products of incomplete combustion trigger a chain of events which may quickly cause great difficulty in respiration. It may culminate into ARDS which would require ventilatory support in ICU and carries a high mortality. High index of suspicion is required to diagnose such cases. Clinical indicators are history of being burnt in an enclosed space, head, neck and upper chest burns, hoarseness of voice, brassy cough, carbonaceous sputum, singing of nasal hairs, alar flaring, tachypnoea, retraction of chest wall, nausea, vomiting, restlessness, disorientation, state of confusion, etc. ABG analysis and carboxyHb levels need to be obtained and monitored. Flexible bronchoscopy is extremely helpful in establishing the diagnosis.

Immediate supportive measures include oropharyngeal suction, administration of 100% humidified oxygen by non-rebreathing mask, bronchodilators, nebulization with heparin/saline/n-acetylcysteine & head end elevation. If there is stridor & respiratory depression, endotracheal intubation should be *immediately* performed. Smaller aperture of paediatric trachea predisposes it to early obstruction. Early intubation is also indicated when a long transfer is anticipated and in cases of large burns which likely will develop rapid airway oedema compounded by large volumes of fluid resuscitation. Intubation becomes difficult after the rapid development of glottic oedema within few hours. Repeated intubation attempts also cause oedema and obstruction which can precipitate cardiac arrest. ET tube must be adequately secured after placement to prevent accidental extubation. Tracheostomy is not preferred due to high rate of infection. However, in situations when gross oedema is already present and there is inability to secure the airway with an ET tube, surgical airway control with TT should be established.

Escharotomy and Fasciotomy

Full thickness circumferential burns around the chest can result in reduced chest wall excursion sufficient to cause respiratory embarrassment. Circumferential eschar over the extremities & digits can cause distal ischaemia & necrosis. Escharotomies should be performed promptly to relieve the compression. It doesn't require any anaesthesia & can be performed bedside with a scalpel or electrocautery to incise full length & depth of the *eschar* (not the underlying fascia). In associated soft tissue injuries to extremity muscles & in electrical injuries, the fascial compartments also become tight due to oedema of the muscles. In such cases, fasciotomies under local analgesia/sedation/short GA should be done to release *all* fascial muscle compartments & maintain the circulation/respiration. Close watch is mandatory for development of any clinical features of vascular/respiratory compromise.

Fluid resuscitation

Infants with >5% TBSA burn, children with >10% TBSA burn and adults with >15% TBSA burn require IV fluid resuscitation to restore the circulating blood volume and maintain electrolyte balance. The starting time for resuscitation is calculated from the time of the injury, not from the time of admission.

Most units all over the world utilize the formulae based on TBSA burned and weight of the patient to estimate the amount of replacement fluid to be infused to manage hypovolaemic shock. Since the capillaries are permeable to even larger molecules in the immediate post-burn period, initial resuscitation is generally done with a colloid free formulae. The commonly used resuscitation formula is *Parkland's formula*, a pure crystalloid formula. It advocates transfusing Ringer lactate solution in a volume 4cc / kg / % burn in first 24 hours. In young children, daily maintenance fluid needs to be added in the form of dextrose saline (0-10kg: 100ml/kg/day, 11-20kg: 1000ml + 50ml/kg/day, >20kg: 1500ml + 20ml/kg/day). Half of the total calculated requirement is given in first 8 hours and the rest as $1/4^{th}$ volume in each subsequent 8 hours period. In the 2^{nd} 24 hours, fluid requirements are approximately half of the first day. Colloids (Hetastarch, Voluven, albumin etc) are added @ 0.3-0.5 cc/ kg/ % burn to minimize hypoproteinaemia. Estimated maintenance fluids also need to be added to maintain the adequate urine output.

However, some units believe that since the linear relation between the weight and surface area does not exist especially in children, use of weight bases formulae result in either under or over-resuscitation especially in smaller and larger percentage of burns. Hence, burn patients should be resuscitated using formulae based on body surface area which can be calculated using standard nomograms or formula BSA (m^2)= [ht(cm) + wt(kg) -60]/100. They advocate administration of 5000 ml/m^2 TBSA burned plus 2000 ml/m^2 TBSA for maintenance fluid to be given over first 24 hours after burn, with half the volume administered over first 8 hours and the remaining during next 16 hours.

Electrical & inhalational injuries require administration of more fluids than thermal burns. Blood transfusions are not required in first 48 hours unless the patient was severely anaemic before sustaining burn injury or any associated soft tissue/ bony injury has caused blood loss. However, after this period, blood may need to be given to maintain Hb level more than 10 gm % & haematocrit between 30-35 %.

Monitoring

Monitoring of the burn patients is vital for effective resuscitation. Formulae described for calculating the amount and rate of fluid to be transfused are mere guidelines. Rate of infusion must be titrated on *hourly* basis as per each patient's clinical response.

There is no single endpoint of resuscitation that reliably and accurately predicts the adequacy of cellular perfusion. Hourly monitoring of urine output with an indwelling urinary catheter is the single most important and the most practical clinical parameter to assess the adequacy of resuscitation. The urine output should be 0.5-1.0 cc/kg/hr in adults, 1-1.5 cc/kg/hr in children and 1.5-2cc/kg/hr in infants. High voltage electrical injury causes myoglobinuria and haemoglobinuria resulting in high coloured urine. Inj sodabicarb is administered to maintain an alkaline pH which increases the solubility of chromoprotiens in urine and prevents their precipitation in renal tubules. Desired urine output in these cases is 2.0cc/kg/hr. Mental status, capillary refill, distal extremity colour also reflect volume status.

Lab investigations advised to monitor the response of the patient are Hb, PCV, blood urea, serum sodium & potassium, serum creatinine, urine specific gravity, base deficit, serum lactate levels, ABG etc. They should serve as the secondary indicators of tissue perfusion and assist in resuscitation. Invasive haemodynamic monitoring (CVP, Swan Ganz catheter etc) should be utilized only for monitoring of extensive burns, inhalational injury, delayed resuscitation, and in patients with already compromised pulmonary / cardiac / renal status.

Fluid creep consequent to volume overload must be avoided. It can lead to compartment syndrome in extremities, increased intraocular pressure, cerebral oedema, pulmonary oedema & right heart failure. Development of abdominal compartment syndrome subsequent to intra-abdominal hypertension almost always proves fatal.

Nasogastric tube should be placed in all intubated patients to prevent gastric dilatation, vomiting and aspiration. Adult patients with burns >25% TBSA, children with > 15% TBSA and infants with >5% TBSA develop paralytic ileus due to neuroendocrine changes and hypovolaemia. Oral intake in such cases is avoided and if stomach is already full, nasogartric tube should be inserted to decompress the stomach and avoid gastric dilatation. After the return of bowel sounds, early enteral feeds are encouraged which increase gut circulation and prevent transmigration of bacteria. Breast feeding should be encouraged in infants.

Burn wound care

The aim of local treatment of burn wound is to prevent microbial colonization and to allow a partial thickness burn to heal spontaneously or else to prepare a full thickness burn for skin grafting.

Wound dressing
The burn wound is cleaned with *dilute* Savlon & saline and mopped dry. Loose, dead tissue is debrided. Large blisters are evacuated & overlying dead epithelium is removed. After applying single layer of paraffin gauze & topical antimicrobial agent, gentle compressive dressing is done over absorbent gauze and Gamgee pads. The dressings are changed daily in extensive burns. Excessive soakage, foul smelling discharge, fever, and undue pain are indications for earlier wound inspection

and more frequent dressing change. In minor burns with minimal soakage & minimal contamination, daily dressing changes are not required. Areas like face, perineum & buttocks are kept exposed after cleaning. The exudate forms a protective cover under which a *partial thickness* wound can heal. Various topical nano-crystalline silver gels and dressings have become popular in past few years. They provide sustained release of highly active silver ions and their bactericidal activity reduces wound bio-burden significantly. Collagen dressings applied directly over second degree burns after debridement reduce the number of dressing changes, lessen pain & soakage and hasten the wound healing.

Topical therapy

Topical antibiotics/ antimicrobials play an important role in minimizing septic complications. Their maximum concentration is on the wound surface, where the risk of exogenous contamination is greatest. Deep wounds become rapidly colonized in 24-48 hours by gram positive cocci & surface colonization eventually leads to deeper invasion of healthy tissues. Topical antimicrobials in common use today are Silver sulphadiazine, Framycetin (Soframycin ®), Nitrofurazone (Furacin®), Povidone iodine (Betadine®), & combination of neomycin, bacitracin & polymyxin B (Neosporin®). A combination of chlorhexidine with silver sulphadiazine (Silverex®) is also available. Silver sulphadiazine 1% cream is the most commonly used topical agent. It penetrates the eschar readily, and is highly effective against many gram negative & gram positive bacteria. It should not be used to treat minor burns where there is no risk of systemic sepsis. Silver nitrate & Mafenide (Sulphamylon®) are infrequently used today.

Burn wound excision

With better understanding of pathophysiology of burns, availability of more effective chemotherapeutic agents & modern monitoring techniques in intensive care management, an aggressive approach has been developed towards the burn wound over past 2 decades. It involves excision of all the burned dead tissues, layer by layer, till a healthy bed is revealed *(sequential excision)*, which is immediately covered with meshed split thickness autograft. If enough autograft skin is not available, skin substitute (biological or synthetic) is used temporarily to cover the excised wound. This approach is undertaken only *after* the patient is haemodynamically stable following adequate resuscitation, and *before* the wound infection has set in. This is usually between 3^{rd}-7^{th} post-injury day. Burn wound excision mandates proper patient selection, an experienced surgical & aneasthesia team, trained OT staff, intensive care facilities & adequate amounts of whole blood. Skin banks and skin culture have proved to be a boon for such patients.

Skin grafting

Split skin autografts are required to cover the raw areas resulting after burn wound excision & after separation of eschar in full thickness burns. The wound has to be adequately prepared to 'receive' the graft. Presence of *Streptococcus beta haemolyticus* is an absolute contra-indication, while that of *Staphylococcus aureus* & *Pseudomonas* is relative contraindication for skin grafting. The grafts are harvested with Humby's knife (or any of its modifications) from unburned areas preferably thighs, legs, arm & forearm. Depending upon the availability, the skin grafts can be applied as meshed / unmeshed sheets / strips / stamps etc. Besides achieving skin expansion, meshing of the graft allows egress of sub-graft fluid & better alignment along the irregular contours.

Pain control

Primary cause of pain in II ° burns is the exposed nerve endings which are extremely sensitive to air currents & friction movements. Pain is greatly contributed by the routine of bathing, wound cleaning, debridement, application of topical agents & skin grafts, dressings, physiotherapy manipulations & splintage. Pain & fear make the patients apprehensive & uncooperative. They need to be comfortable to facilitate the work of nursing & dressing staff & physiotherapists. Pain relief and sedation must be preceded by correction of hypovolaemia and hypoxia which cause restlessness in a burn patient.

Morphine (0.5mg/kg iv 2-4hrs)/pethidine, pentazocine–promethazine combination administered slow iv is quite effective in controlling resting as well as procedural pains. Midazolam and Ketamine (oral / i.m. / i.v.) have also been effectively used in the management of burn patients for obtaining analgesia for variety of above mentioned procedures. Oral paracetamol, ibuprofen and nimuselide combinations provide adequate control of resting pain in minor burns.

Systemic chemotherapy

Patients with extensive burn injury are particularly susceptible to burn wound sepsis. Burn wound provides a large, warm, moist & protein rich medium for growth of micro-organisms from exogenous as well as endogenous sources. Sepsis remains the leading cause of death in burns. The most common sites for primary infection in burn patients are the burn wound, lower respiratory tract, urinary tract and the blood stream. Bacteriological monitoring by wound surface swabs should be a routine. The culture of tips of all invasive devices and culture of blood is recommended in cases of sepsis. Burn wound biopsy has also been utilized to establish infection by quantitative estimation of the bacteria (>10^5 bacteria/ per gram of tissue).

Bacteria commonly isolated from a burn wound are *Staph. aureus Strept. faecalis, Klebsiella, Proteus, E coli & Pseudomonas*. Acetinobacter, fungi & viruses are also being increasingly isolated. Although debatable, routine use of prophylactic antibiotics is generally not recommended in many burn units as it leads to rapid emergence of resistant strains. Fever, tachypnoea, tachycardia, diarrhea, abdominal distention, leucocytosis, altered sensorium, any features of local wound sepsis like sub-eschar haemorrhage, bluish-purple necrotic areas in wound etc. are considered as indications for initiating systemic antibiotic therapy. They are started in broad spectrum combinations, empirically, depending on the resident flora of a particular burn centre, and later modified as per the culture reports. They are administered in the maximal therapeutic dose & stopped after 7-10 days. Antibiotics useful in burns are penicillins, cephalosporins, aminoglycosides, quinolones, carbapenems etc.

Nutritional support

A major burn injury with / without associated sepsis induces considerable hypermetabolic response which leads to increased glucose production, insulin resistance, lipolysis & muscle protein catabolism. Close attention to nutritional needs is critical to prevent excessive protein breakdown, delayed wound healing, immune suppression & an increase in infective complications. The patient requires very high calorie & protein intake to restore the deficit, & to promote a positive nitrogen balance. Use of anabolic steroids & growth hormones has been suggested to reduce muscle catabolism & weight loss.

There is great deal of controversy on what, when & how much the burn patient should be fed. Many formulae have been described to determine the calorie & protein requirements. Besides calories, an adequate amount of proteins need to be given to maintain positive nitrogen balance, to prevent weight loss, to improve resistance and survival. Supplements of vitamins and trace elements also hasten the wound healing.

Enteral route, if available, should always be preferred for providing nutrition. Patients who are unable to take orally or have inadequate dietary intake should be given nasogastric tube feeds. Parenteral alimentation is necessary if patient is having nausea, vomiting or diarrhea. It has been established that early enteral feeding preserves gut mucosal integrity, improves intestinal blood flow and motility, minimizes translocation of gut bacteria and can minimize the post-burn hypermetabolic response. Parenteral supplementation with 10-20% dextrose, aminoacid & lipid solutions is also recommended. Total parenteral nutrition (TPN) is occasionally necessary, but it requires additional vascular access with its concomitant risks.

Physiotherapy & Rehabilitation

Physiotherapy & rehabilitation efforts should begin as soon as feasible after sustaining the burn injury. The goals are to limit/prevent loss of motion, minimize/prevent anatomic deformities, and return the patient to work as early as possible. Positional changes in bed to prevent development of decubitus ulcers, making the patient sit up & instituting chest physiotherapy to prevent hypostatic pneumonia, encouraging early ambulation to minimize the risk of thromboembolism, and application of splints to keep the burned hands in functional position are to be undertaken during the acute/initial phase. Once the patient is haemodynamically stable (and if the burn wounds permit), active & passive stretching of various muscles putting the limb joints through their range of motion and applications of splints is instituted.

Oral anti-histamincs are prescribed to control post burn itch which may be distressing in spontaneously healed areas and skin graft donor sites. Gabapentine and pregablin have also proved to be effective in controlling the itch. Silicone inserts, pressure garments for continuous use for 9-12 months, and therapeutic massaging of the healed areas with bland oil /cream is advised. All this routine has to performed, supervised, taught & followed up regularly by occupational & physiotherapists.

Burn reconstruction

Although contractures, unsightly scars, vitiligo/hypopigmentation, post burn losses /amputations, scar hypertrophy, psychological sequelae etc. comprise the important complications of thermal trauma, the majority of functionally crippling deformities are the result of severe post burn contractures. Despite the advances in past few decades in reconstructive techniques like tissue expansion, prosthetic joints, microsurgical procedures etc., the time honoured standard procedure of release of contracture (with or without excision of scar) followed by skin grafting, coupled with appropriate post-operative management (massage, splints & physiotherapy) still remains the cornerstone of all surgical attempts to make the victim *functionally independent* and *socially acceptable*. Correction of multiple contractures needs to be judiciously staged and sequentially planned keeping in consideration the patient's needs, anesthetists requirements, availability of skin graft donor sites etc. Multiple procedures may be required under LA as well. It is beyond the scope of this article to even briefly review the reconstructive techniques available today for correction of myriad of post-burn deformities.

Suggested readings:

1. **Settle John AD, Edn. Principles and Practice of Burns Management. Churchill Livingstone;1996**
2. **Herndon David N, Edn. Total Burn Care. Edn, Saunders Elsevier; 2007**
3. **Sood Rajiv, Edn. Burn Surgery-Reconstruction and Rehabilitation. Saunders Elsevier; 2006**
4. **Sarabhai S, TiwariVK, Goel A, Gupta LC, Edn. Principles and Practice of Burn Care. Jaypee; 2010**

Tissue Expansion

P.S. Bhandari

Tissue expansion is a technique used by plastic and restorative surgeons to cause the body to grow additional skin or other tissues. Tissue expansion is a novel technique of regenerating donor tissue in situ without compromising innervation, vascularity, or external physical appearance. The human skin is plastic nature. It can be expanded is to grow extra skin through controlled mechanical overstretch. It creates skin that matches the color, texture, and thickness of the surrounding tissue, while minimizing scars and risk of rejection. The surgeon can take advantage of this plasticity whenever there is a need of reconstructive or aesthetic surgery.

Background

The concept of soft tissue expansion came from distraction techniques used for bone lengthening as early as 1905. Neumann (1957) became the first surgeon to use expansile implant. His work remained unrecognized till 1976 when Radovan performed tissue- skin expansion with silicone prosthesis. Shortly thereafter in 1982 Eric Austad produced a self-inflating device that used osmotic gradients driven by salt placed within the expander.

Physiology of Tissue Expansion

The expansion of skin depends upon its unique character of elasticity. This uniqueness of skin depends mainly on the twin fibrous networks of collagen and elastin which constitute the bulk of the dermis. In the relaxed state the collagen fibers are markedly convoluted and when the skin is stretched the convolutions straighten out. As the load increases, skin stretches and an increasing number of fibers become aligned in the direction of the stretching force, until finally there is a structure of parallel fibers.

Tissue expansion can be explained through "creep" phenomenon where, when the skin is stretched and the stretching force is kept constant, the skin continues to extend. In "mechanical creep" there is

disruption of gap junctions, cell stretches and the collagen fibers become arranged in a parallel fashion. Actual cell proliferation takes place in “biological creep”.

By far the most common method, the surgeon inserts the inflatable expander beneath the skin and periodically, over weeks or months, injects a saline solution to slowly stretch the overlaying skin which remains stretched due to “creep” phenomenon

Biology of Tissue Expansion

Epidermis shows initial significant thickening which returns to initial levels in 4-6 weeks. There is rapid decrease in thickness of dermis during expansion. Hair follicles are distracted but there is no degeneration. Muscle shows significant atrophy that returns to normal after removal of prosthesis. There is decrease in bone thickness and volume beneath the expander and increase of these tissues at the expander periphery. A capsule is formed around the prosthesis with rich vascular plexus within its collagen. Angiogenesis occurs in response to induced ischemia of the expanded tissues with increased expression of vascular endothelial growth factor.

Advantages

- Reconstruction with tissue of a similar colour and texture to that of the donor defect.
- Reconstruction with sensate skin containing skin appendages
- Limited donor-site deformity.

Expander Types

Several types of tissue expanders exist, based on shape, size, and type of filling valve. In terms of shape, they follow three basic patterns: round, rectangular and crescent. Expander volumes have a wide range and vary according to the anatomic site. Saline is delivered in a controlled fashion via the valve port, which is either integrated into the prosthesis or a remote port connected to the device by silicone tubing.

Basic Principles

The key to successful expansion is meticulous planning. The donor tissue must be free of infection, previous scars or trauma to prevent implant failure or extrusion. If possible the expander is placed through an incision within the lesion to be excised. Partial fill of the expander at the time of placement assures that the expander is properly positioned and without surface folds. Serial inflation usually starts 1–2 weeks later and is done at weekly intervals. Individual inflations proceed until the patient experiences discomfort or blanching of the overlying skin. Expansion is stopped when the amount of tissue gained is sufficient to permit adequate reconstruction.

Applications of Tissue Expansion

Tissue expansion has its application in the reconstruction of head and neck, breast, chest, trunk and extremities, expansion of full thickness grafts and flap expansion. But the maximum usage has been found in the reconstruction of breast and scalp.

Breast

Expanders have found roles in breast surgery in postmastectomy reconstruction and habilitation of congenital anomalies. It is a two stage procedure where the tissue expander is placed in the first stage via incision through the mastectomy scar, periareolar or inframammary incisions. In the second stage the expander is replaced with a permanent implant. The expander is located in submuscular plane (beneath pectoralis major and serratus anterior); subpectoral dual plane (upper half beneath pectoralis and lower half subcutaneous); subpectoral with acellular allogenic dermal matrix covering the lower pole. After volumetric symmetry with the opposite side, hyperinflation is carried out to create ptosis.Expanders are replaced by implants once the desired expansion is achieved. Expanders are used as “spacers” in the correction of congenital breast anomalies and replaced with permanent implants once the patient reaches maturity.

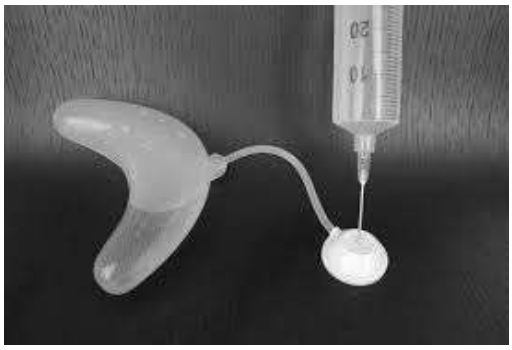
Scalp

Scalp reconstruction has three general indications: large congenital nevi, scar and skin graft alopecia and as an adjunct to craniofacial reconstruction. Tissue expansion itself does not induce proliferation

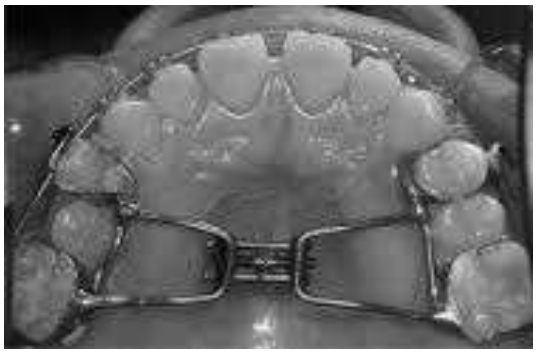
of hair follicles, rather existing follicles are redistributed. Expander is placed in the subgaleal plane. Expansion is initially uncomfortable and so it is better to use frequent small saline injections than to use infrequent large injections. Some erosion and depression of the skull may be seen in children so expansion should best be delayed until they are approximately 1 year of age.

Complications

- **Haematoma**
- **Infection**: perioperative introduction is the most common cause; warrants prosthesis removal;
- **Exposure of the expander :** prosthesis needs to be removed in early exposure of implants; in cases of late exposure, conservative management with topical antibiotics and frequent small inflations usually is sufficient.
- **Pain**
- **Neurapraxia**
- **Pressure effects on surrounding tissue.**



Croissant tissue expander



Expansion of maxilla

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Hirschsprung's Disease

Satish Kumar Aggarwal

Hirschsprung's disease (HD) is a surgical cause of constipation in children. It is important to differentiate it from other common and non-surgical causes such as functional constipation. This chapter highlights the basic pathology and clinical presentation of HD in neonates and infants. A plan of diagnosis and management as appropriate t post graduate students of surgery and practising general surgeons is presented.
Synonyms: Congenital Megacolon, Congenital Aganglionosis

Hirschsprung's disease (HD) was first described in 1886 by a Danish physician Harald Hirschsprung. It was a description of few cases of constipation in children in association with dilatation of sigmoid colon. The interesting aspect of the report was that the dilated sigmoid was thought to be the offending factor. It became evident later that actually the offending factor was a functional obstruction in the rectum due to absence of ganglion cells. Dilatation of the sigmoid was an after effect of a distal obstruction.

Pathology

Normally the neural crest cells (ganglion cells) of the enteric nervous system migrate cranio-caudally to innervate the entire gut. Rectum is the last to receive its share. Failure of this migration in the intra-embryonic life results in aganglionosis, usually of the most distal gut i.e. rectum – leading to the most common form of HD referred to as classical or rectosigmoid HD. Less commonly sigmoid and descending colon are also involved (Long segment HD). The entire colon including the terminal ileum can also be involved (Total colonic Aganglionosis. Very rarely the entire gut may be involved.

In the most classical form i.e. rectosigmoid disease the rectum fails to relax to accept a faecal bolus causing functional obstruction. The proximal normally ganglionated sigmoid colon tries to overcome the obstruction and in the process becomes dilated. The rectum remains spastic.

Clinical features

The disease can present at birth (most common), infancy, and childhood and rarely in adults. Nearly 80% cases should be diagnosed in neonatal period in the current era. The presentation is in the form of:

1. Failure to pass first meconium within 24-48 hours is the most important presentation. In term babies the first meconium should be passed within the first 24 hrs. In preterm babies it extends to 48hrs. The first meconium is delayed and often suppositories are required to facilitate passage of meconium.
2. Progressive abdominal distension- It is soft gaseous distension with bulge in the flanks also due to colonic distension.

3. When rectal stimulation is done- either by a digital examination/ suppository or enema the distension is relieved with passage of meconium and gas.
4. Uncommonly the distension may persist despite rectal stimulator (long segment disease, TCA) then the neonate may develop features of small bowel obstruction (bilious vomiting, visible loops, multiple air fluid levels on abdominal X-ray) if left untreated- colonic perforation because of dilatation under pressure may occur.

Infants and Toddlers: Progressive constipation since early infancy (within 1st month) is a typical presentation in infants and toddlers. Usually there is a history of delayed passage of meconium after birth, need for suppositories to pass meconium in the first week. Constipation is progressive with need for increasing doses of laxatives/ enemas etc. There is no straining, and no perianal soiling. Abdomen is bloated. Appetite is poor.

Older children: Progressive constipation, need for laxatives, abdominal distension and growth failure are common. Nutritional deficiencies may be evident. The child is generally hypoproteinemic.

Diagnostic Investigations

Contrast enema and **rectal biopsy** are the two most important investigations. Anorectal manometry is useful in select cases where ultra-short segment HD (also known as internal sphincter achalasia) is suspected.

Contrast enema should be performed in lateral position, using an unlubricated plain tube (end opening plain catheter- not a Foley with inflated balloon), with buttocks pinched. Small volume of water soluble non-ionic contrast (Iopaque) should be injected slowly under fluoroscopic control to fill the rectum and sigmoid. A typical transition zone is seen in H.D. as shown in the figure. The aganglionic rectum appears small in calibre. Just above this a funnel shaped area is seen which is hypo-ganglionic. Proximal to that the dilated sigmoid which is normally ganglionated is seen. The study is stopped as soon as the transition zone is evident. It is a myth that enemas and rectal examination should be stopped 24hrs before contrast enema. Transition zone does not disappear following rectal stimulation, enemas and washouts.

Rectal Biopsy: Different types of rectal biopsy are:

1. ***Full thickness rectal biopsy*** (FTRB): Done under G.A. Full thickness of rectal smooth muscle is taken as a biopsy 2.5 and 3.5cm above the anal verge. Biopsy from anal canal (area of internal sphincter) should be avoided as it is normally also hypo-ganglionic. It is the most informative biopsy as it may show both the Meissner & Aurbachs plexuses in the rectal smooth muscle.
2. ***Punch biopsy***: Mucosa and good chunk of muscle can be biopsied without anaesthesia using a punch biopsy forceps (3mm or 5mm laparoscopic biopsy forceps or Yeoman's ENT forceps). It is more suitable for younger children and infants as it can include good amount of muscle. A possible complication is perforation.
3. ***Suction rectal biopsy***- Specially designed guns are available to take small biopsy from mucosa and submucosa and possibly small amount of muscle. Generally it is suitable for neonates. The pathologist should have expertise and experience to accurately report on small tissue containing very little muscle.

Diagnosis of HD on biopsy is made by-

1. Routine H& E staining: Ganglion cells are absent in all plexuses- mucosal, submucosal and both the muscular plexuses. There is an all or none law. If mucosal and submucosal plexus shows absence of ganglion cells, it will be absent in muscular plexus also. This is the basis for diagnosis by suction biopsy which may not include muscle layer. The density of ganglion cells is highest in muscle plexus hence it is easier for the pathologist to report on FTRB or punch biopsy as compared to suction biopsy.
2. AChE staining (Histochemistry): The tissue in HD shows high Acetyl choline esterase activity.
3. Monoclonal Antibodies (Immunohistochemistry): Monoclonal antibodies against certain neural components can be stained with special techniques. D7 is one such monoclonal antibody.
4. Electron Microscopy is useful for smooth muscle disorders.

In practice the H&E staining is the most commonly used tool.

Anorectal Manometry can also be used. Generally it is useful if there is diagnostic difficulty between HD and functional constipation. Typical feature of HD is absent internal sphincter relaxation reflex (ISRR). Caution: In sick neonates it may show false positive diagnosis (Sick ganglion syndrome). It is however diagnostic in internal sphincter achalasia, which cannot be diagnosed by contrast enema.

Management

Neonate: Once the diagnosis is confirmed the baby is put on daily rectal washouts/ enemas to help decompress bowel. Oral feeds are established. Once normal growth is demonstrated a primary definitive pull through is performed. This approach avoids the use of parenteral nutrition and at the same time establishes oral feeds till such time that the child is ready for definitive surgery without much risk of anaesthesia and major surgery. Most classical cases fit into this schema of management. The parents learn the technique of washouts and carry out at home.

If rectal washouts fail i.e. if decompression is not achieved, child remains distended and feeds can't be established, a staged approach is followed i.e. a colostomy is opened in the first stage. Definitive pull through is performed few weeks later.

Older child: When the disease is neglected for a long time the colon proximal to aganglionosis dilates very much. Primary pull through, though possible, may not be the preferred treatment. It is sometimes better to open a stoma (colostomy), wait for dilatation to decrease and then perform a pull through several months later.

Opening a colostomy for Hirschsprung's disease:

1. ***Transition zone colostomy***- The colostomy is opened at transition zone/ just at the distal limit of normally ganglionic dilated colon. A biopsy is taken from rectum at peritoneal reflection (to prove the diagnosis). Another biopsy is taken from nearly 5 cm proximal to colostomy (to level ganglionic bowel for further pull through). During definitive pull through the colostomy is mobilised and the ganglionic bowel pulled through. This makes a two stage treatment possible.
2. ***Hartman procedure with end colostomy***- The aganglionic bowel is divided at peritoneal reflection and rectal stump is closed, distal rectum and dilated portion of sigmoid is resected. End stoma is made in normal calibre sigmoid/ descending colon. Specimen is inspected for ganglionic cells at distal and proximal ends. In the second stage the colostomy is pulled down through retro rectal space in Duhamel fashion.
3. ***Right transverse colostomy***- if the treatment is planned in 3 stages, a right transverse colostomy (to the right of middle colic vessels) is opened. Pull through is performed few weeks later without disturbing the colostomy. Colostomy is closed 2-3 months later.

Definitive pull through operation

The currently popular operations are:

1. ***Laparoscopic Assisted Trans Anal Pull Through***: the operation is performed in 2 parts -
   (i) *Laparoscopic*- Through 3 or 4 ports a frozen section biopsy is sent from expected ganglionic site (just proximal to transition zone). The descending colon is mobilised for pull down. Pelvic rectum is dissected close to its wall in the pelvis, behind the bladder. The dissection is kept just next to the rectal wall so as to avoid damage to Hypogastric nerves behind the bladder.
   (ii) *Trans anal*- Retraction sutures are placed on anal verge to expose the anal canal. A circumferential incision is made in the mucosa nearly 0.5cm above dentate line. Submucosal dissection is carried out upwards. When this dissection reaches the mobilised (laparoscopically) rectum in the pelvis the muscle starts prolapsing through the anus. The incision is made in the muscle to pull down the mobilised colon to the level of normal ganglion cells as decided by frozen section biopsy. Colon is transacted at the level of normal ganglion cells and anastomosed to the anal canal at the site of mucosal incision after dividing the excess muscle cuff above it in midline posteriorly.

2. ***Laparoscopic assisted Duhamel*** Pull through: Duhamel Pull through is a retro rectal pull through wherein the normally ganglionated colon is brought down to anal canal through the retro rectal space and delivered through the anal canal through a 'smile' incision in posterior wall of rectum. A long S-S colorectal anastomosis is performed by a linear cutter stapler. The rectal

stump at peritoneal reflection is either closed (Classical Duhamel) or anastomosed to the pulled colon (Martin modification).

The abdominal part of operation i.e. mobilisation of colon, development of retro rectal space and closure of rectal stump can be performed laparoscopically. If a previous Hartman procedure had been done, laparoscopy assisted Duhamel becomes very easy as the colonic resection and closure of rectal stump has already been done in the first stage.

Duhamel operation is a versatile operation which retains the rectum and hence the rectal sensation, storage and better bowel function. At the same time the posterior wall becomes normally ganglionic because of long side to side stapled colorectal anastomosis between the part of rectum and anterior wall of the pulled through colon.

Other operations

Orwar Swenson (1949) described the first operation for HD. It involves open/laparoscopic assisted complete excision of all aganglionic bowel and an anastomosis between normally ganglionated bowel and the anal canal. Many surgeons still favour it although now laparoscopy has also made inroads to help the same meticulous dissection close to the rectal wall.

Soave operation (Boley's modification): Also referred to as Endorectal pull through (ERPT). In this operation the rectum is not dissected at the muscle level, but a mucosal sleeve is developed by submucosal dissection. The pulled through colon is pulled through the muscular sleeve and anastomosed to the anal canal.

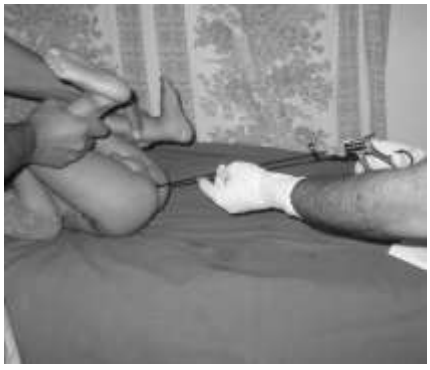
Advances in techniques

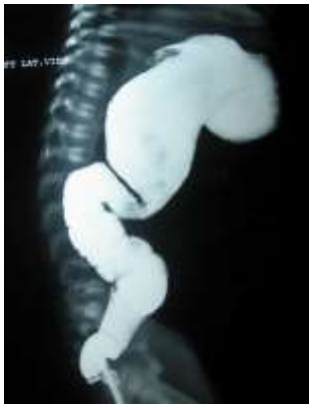
1. Laparoscopic techniques have become popular for treatment of H.D.
2. Gradual transition has happened from a three staged operation to two staged and then to single stage operation.
3. More and more cases are diagnosed in neonatal period.
4. Early definitive pull through at few weeks is fast becoming common.
5. Early pull through has become more common.
6. 5mm roticulating GIA staplers will be available shortly to make laparoscopic Duhamel an easy option in small babies as well.
7. 3 mm vessel sealer will be available shortly, which will ease out laparoscopic mobilisation of colon in babies and infants.

Table showing differentiation of functional constipation from HD

	Functional Constipation	**H.D.**
1. Onset	At weaning time	Since birth
2. Straining	Yes	No
3. Perineal soiling	Yes	No
4. P/R examination	Rectum loaded with stools till the verge.	Faecal loading felt above the rectum. Rectum empty.

Punch biopsy technique:





Recent advances in management of carcinoma rectum

NK Shukla

Introduction

Colorectal cancer constitutes third common cancer worldwide. 40,000 new cases of rectal cancer were diagnosed in past one year in US. In last three decades many advances have taken place in the management of rectal cancer including better understanding of molecular biology, advances in diagnostic and staging modalities, changing concepts of surgical resection as understanding zone of upward spread, concept of total mesorectal excision and higher sphincter preservation. Impressive advances have taken place in the field of adjuvant therapy both radiation and chemotherapy with development of new drugs and evolution of targeted therapy.[1]

Advances in molecular biology

These advances have led to predict the response to adjuvant therapy and development of targeted agents. They include DNA sequencing of microsatellite instability, detection of oncogenes, proteins and growth factors. KRAS and P53 positivity indicates poor prognosis. Vascular endothelial growth factor receptor (VEGFR) and epithelial growth factor receptor (EGFR) are targeted by monoclonal antibodies leading to the development of Bevacizumab, Cetuximab and Panitumumab. Tyrosine kinase receptor is targeted by agent like Regorafinib.

Changing concepts in surgical resection

Treatment of early cancer (T1N0M0)

Early lesions are treated by surgery in form of transanal local excision, transanal endoscopic microsurgery (TEMS) and endoscopic mucosal resection (EMR). The selection criteria for local surgery includes superficial tumors less than 3 cm, located in middle and lower rectum, well differentiated histology, no neurovascular invasion and compliance with aggressive post operative surveillance. Currently EMR is the most preferred approach.[2]

Treatment of locally advanced cancer (T2-3, N1-3, M0)

Surgery is the cornerstone of curative therapy for locally advanced cancer. Primary goal is complete removal of primary tumor and secondary goal is preservation of anorectal sphincter function and bowel continuity whenever possible.

Principles of resection

Wide excision of the primary tumor achieving histological negative margins proximal, distal and circumferential along with total mesorectal excision is performed. This is done along with resection of lymph nodes up to inferior mesenteric artery pedicle. The preservation of anorectal sphincter is only done if histological negative distal margin can be achieved.

Distal margin

Earlier recommended distal margin was 5 cm hence there was high rate of abdominoperineal resection (APR). Recently mostly accepted distal margin is 2 cm along with TME. With the improvement in surgical techniques and incorporation of neoadjuvant chemotherapy (CT) and radiotherapy (RT) a negative margin of 1 cm or less is acceptable and it compares 2 cm margin in terms of loco regional recurrence rate.[3,4]

Circumferential resection margin (CRM)

To achieve a negative CRM total mesorectal excision (TME) including complete removal of mesorectal fascia enveloping fat pad around the rectum containing terminal branches of IMA, lymphatics and perirectal lymph nodes. TME has become standard of surgical care for cancers of middle and lower rectum. Sharp meticulous dissection is done in the avascular (Holy) plane between presacral fascia and mesorectal fascia. Blunt dissection previously performed can damage mesorectal fascia leading to higher loco regional recurrence. Distance of mesorectal fascia from the tumor 2 mm or less it is called threatened involvement and is an indication for neoadjuvant treatment. A positive CRM leads to higher loco regional recurrence and poor five-year survival. [5,6]

The length of mesorectum removed beyond the tumor margin should be 3 to 5 cm.[7] For tumors of upper rectum TME includes removal of mesorectum 5 cm distal to the tumor, for middle and lower rectum complete TME is done till the pelvic floor. TME with negative CRM improves loco regional control rate to 4-7% and better survival.[8] TME also preserves pelvic autonomic nerves and decrease genitor urinary dysfunction. According to NCCN and ASCO guidelines at least 12 lymph nodes should be removed with TME.[9]

Sphincter sparing resection

It is indicated for histologically proven distal resection margin. Procedures include low anterior resection (LAR) and very low (ultra) low anterior resection. Temporary diversion stoma decreases clinically relevant anastomotic leaks.[10]

Abdominoperineal resection (APR)

APR is indicated if histologically negative distal resection margin cannot be achieved. It is also indicated as salvage surgery for recurrence of sphincter saving procedure and local resection.

Laparoscopic assisted APR and LAR

Radical surgery for rectal cancer can also be done by minimal invasion surgery. The procedure is safe even after neoadjuvant CT/RT.[11] The quality of oncological resection is equal to open surgery. It causes less post operative ileus and pain. The length of hospital stay is decreased.

The colorectal cancer laparoscopic or open **trial COLOR II** [12] has shown similar completeness of resection, equivalent rates of positive lymph nodes, CRM and median tumor distance of distal margin.

Robotic assisted resection of rectum

With this emerging technology and high quality three dimensional vision the rectal resection can be safely done. TME is safe and feasible. Less postoperative pain and faster recovery are advantages of the procedure but high cost, long intraoperative set up time and long procedure time are disadvantages.

Exenteration procedures

In advanced rectal cancers with involvement of urinary bladder, prostate, uterus and vagina exenteration procedures are recommended. If posterior or total pelvic exentration can be done provided the tumor is not invading the lateral pelvic wall and there are no internal iliac lymph nodes.

Cytoreductive surgery with hyperthermia intraperitoneal chemotherapy (HIPEC)
This procedure has recently shown promising results in peritoneal metastasis from rectal cancer.

Neoadjuvant therapy in the combined modality approach in rectal cancer

Though the surgical resection is cornerstone of managing locally advanced carcinoma rectum, last two decades have shown better results when it is combined with neoadjuvant therapy. Indication of neoadjuvant therapy include

1. Presence of T3 or T4 tumors
2. Presence of lymph nodes in the mesorectum as shown by MRI or TRUS
3. Invasion of mesorectal fascia or threatened mesorectal invasion neoadjuvant therapy decreases positive CRM
4. Neoadjuvant therapy can increase the sphincter preservation. It can convert candidates thought for APR to sphincter preservation by 20-40%. In **German trial** sphincter preservation with neoadjuvant therapy was 39% as compared to those without neoadjuvant CT/RT (19%).[13]

Neoadjuvant RT / Preoperative RT
In Swedish trial short course preoperative radiotherapy in the dose of 25Gy in 5 fractions over one week with rectal resection after 3-6 weeks compared with no RT have shown significant improvement

in local control (89% versus 73%) and overall survival (58% versus 48%).[14] **The Dutch trial** have also shown better results with preoperative short course RT with local recurrence of 5% versus 11%.[15]

Neoadjuvant CT-RT versus postoperative CT-RT

The German rectal cancer trial has also shown that neoadjuvant CT-RT gives better results as compared to postoperative CT-RT, local recurrence rate 6% versus 13%, DFS 68% versus 65%.[13]

Preoperative RT versus neoadjuvant CT-RT

Polish trial has compared neoadjuvant CT-RT with preoperative RT and has shown higher pathological CR rates with neoadjuvant CT-RT (16% versus 1%), CRM positive rate 4% versus 13% and loco regional recurrence rate 9% versus 14% indicating superiority of neoadjuvant CT-RT as compared to preoperative RT.[16] The radiotherapy was given 45 Gy in 25 fractions over 5 weeks and surgery was performed after 4-6 weeks.

The drugs used for NACT-RT were 5FU which is the gold standard and newer drugs like oxaliplatin, irinotecan, capecitabine. The targeted therapy along with chemotherapy gives better results. Monoclonal antibodies like Bevacizumab, Cetuximab and Panitumumab are used.

Metastatic rectal cancer

Usual metastatic site is liver. The metastasis can be synchronous or metachronous. In synchronous metastasis if resectable primary the options are

A. Neoadjuvant CT-RT followed by surgery for both primary and metastasis followed by adjuvant chemotherapy
B. Surgery for the primary rectal tumor followed by chemotherapy and letter removal of liver metastasis
C. Chemotherapy with targeted therapy for 2-3 moths than surgical resection of primary and metastasis followed by adjuvant chemotherapy.

Summary

The recent advances in the management of rectal cancer have taken place by improvising surgical resection and addition of neoadjuvant chemotherapy, radiotherapy and targeted therapy. TME has become the standard practice in all locally advanced rectal cancer patients. Distal resection margin has receded from 5 cm to 1 cm provided it is histologically negative. Importance of negative CRM has been realized. Incorporation of neoadjuvant chemotherapy has decreased local recurrence and decreased distal resection margin thereby increasing sphincter saving surgery and quality of life. Laparoscopic assisted APR and LR emerged as alternative approach to open surgery. Targeted therapy has added efficacy to chemotherapy. Thus management of rectal cancer has moved from a pure surgical treatment to a real multimodality management.

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Follow Up in Colorectal Cancers

R. S. Mohil, Nikhil Bansal

Colorectal cancer is one of the most common malignancies, with an estimated age-adjusted annual incidence in North America of 75 cases per 100,000 population (1-3). About 75% of newly diagnosed cases have the tumor confined to a portion of the bowel and regional lymph nodes. Complete removal of the tumor en bloc with a portion of normal bowel along with mesenteric and regional lymph nodes is considered a curative resection. In spite of this curative resection, approximately half the patients develop recurrent disease, and their median survival does not exceed two years (1-4). Most of these recurrences occur in patients who at initial staging had a tumor invading across the bowel wall causing perforation of the bowel, adhesion, invasion of neighbouring organs (stage IIb disease), or lymph node metastases (stage III disease). Besides disease recurrence, patients with colorectal cancer are considered to be at a higher risk for developing a second or metachronous bowel cancer (5,6).

The primary goal of surveillance following curative resection of colorectal cancer is to identify recurrent disease at an asymptomatic stage when it is amenable to re-resection and to improve survival. To achieve this goal, patients are screened for early recurrent disease and a second colorectal cancer, with the intent of a second curative surgery. Although curative treatment remains primarily surgical, only a small percentage of patients are amenable to re-resection, and an even smaller percentage realize a definitive cure(7).In response, some authors advocate a minimalist approach (8). Such an approach may not be justified as there is increasing evidence to suggest that a small but recognizable subset of patients benefit from surveillance(7).In a recent RCT of 1202 patients on intensive surveillance using either CEA or CT imaging in Stage I –III lead to detection of recurrent or metastatic disease which had higher chance of curative intent resection than in group on screening based on symptoms alone. However there was no difference in survival between the two groups (18.3% vs. 15.9% 95% CI -2.6% - 7.1%) (7).

Common sites of recurrence are shown in Table 1. As no single screening test is best for all sites of recurrent disease and second colorectal cancer, a combination or package of tests is commonly used. The screening tests are directed to areas of potential disease and conducted at pre-established intervals. An analysis of 20,898 patients in 18 trial showed that the incidence of recurrent disease occurs at an exponential rate with over 80% of recurrences occurring in the initial3years from date of surgeryand 95% occurring by 5 years. After this it reaches a plateau (1-3). Therefore all the screening tests for recurrent disease are conducted frequently during the first three to five years and infrequently afterwards. Screening tests for second colorectal cancer, on the other hand, must be done at equally spaced intervals for life because the incidence of second colorectal cancer occurs at a constant cumulative rate of 3% every six years (5,6).

Table 1: Estimate of the percentage of patients with recurrence at five years by site of recurrence

Site of Recurrence	Percent of Patients with Recurrence at 5 Years by Site of Initial Tumour*	
	Colon	**Rectum**
Liver	35	30
Lung	20	30
Peritoneal	20	20
Retroperitoneal	15	5
Peripheral Lymph Nodes	2	7
Other (brain, bones)	<5	<5
Loco-regional	15	35
Second or metachronous colorectal cancer	3	3

Regular surveillance can also lead to the identification of other health problems and provides a forum for discussion of new treatments, relevant changes in family history, and genetic issues. Additional benefits include the detection of postoperative problems (wound and stoma problems, sexual and/or urinary dysfunction), facilitation of audit for individual surgeons, the assurance of quality control for employers, and the provision of greater psychological support for the patient (9). In general, patients derive a sense of well-being and reassurance with regular follow-up (10). Should problems arise, there is clear recognition of whom to notify.

On the down side, some patients may experience anxiety prior to their visit. Furthermore, particularly with more intense surveillance regimens, there is a greater potential for false-positive test results that may provoke further anxiety and the costly use of additional resources. On the whole, however, studies have shown that patients are very willing to under go follow-up and experience no decrease in quality of life from frequent testing (11).

Patients treated with appropriate resection for stage I colon cancer generally have a 5-year survival rate of approximately 90%. The 5-year survival rate for patients with stage II colon cancer treated surgically is approximately 75%.The survival of stage III patients, with lymph node metastasis, is approximately 50%, and patients with stage IV disease (distant metastases) have a poor prognosis, with a 5-year survival of less than 5%.

Follow-up, surveillance, and secondary prevention measures for survivors of CRC, stages II and III. For stage I or resected metastatic disease, there is minimal data to provide guidance. The Cancer Care Ontario (CCO) Guideline from Canada on Follow-up Care, Surveillance Protocol, and Secondary Prevention Measures for Survivors of Colorectal Cancer have been arrived after a very comprehensive review of the literature (**Figure 1**). These were reviewed and endorsed by the American Society of Clinical Oncology (ASCO) in year 2013.

The CCO addressed **six questions** of which the sixth is not relevant outside Ontario, Canada.

1. Which evaluations (e.g., colonoscopy, computed tomography [CT], carcinoembryonic antigen [CEA], liver function, complete blood count [CBC], chest x-ray, history, physical exam) should be performed for surveillance for recurrence of cancer?
2. What is a reasonable frequency of these evaluations for surveillance?
3. Which symptoms and/or signs potentially signify a recurrence of CRC and warrant investigation?
4. What are the common and/or significant long-term and late effects of CRC treatment?
5. On what secondary prevention measures should CRC survivors be counselled?
6. Are there preferred models of follow-up care in Ontario, i.e., should patient follow-up be done by a medical oncologist, radiation oncologist, surgeon, advanced practice nurse, physician assistant, or primary care provider (e.g., family physician, nurse practitioner, family practice nurse)?

1. Which evaluations (e.g., colonoscopy, computed tomography [CT], carcinoembryonic antigen [CEA], liver function, complete blood count [CBC], chest x-ray, history, physical exam) should be performed for surveillance for recurrence of cancer?

2. What is a reasonable frequency of these evaluations for surveillance?

- Every 3-6months for 2years
- Every 6months for a total of 5years

CEA testing

- Baseline
- Every 3-6months for 2years
- Every 6months for a total of 5years

The ASCO guideline (12) recommends a history and physical examination every three to six months for the first three years and then every six months for two more years. After the fifth year, the schedule for further examinations is at the discretion of the physician. ASCO also recommends postoperative serum CEA testing every three months in patients with stage II or III disease, for at least three years. The recommended schedule of the NCCN (4,5) and Australian (13) guidelines for physical examinations for up to five years is similar to that of ASCO, except that the frequency decreases after two years, and both recommend testing CEA in every physical examination session. The updated Programme in Evidence Based Care (PEBC) guideline recommends testing serum CEA and a physical examination when the patient is symptomatic or every six months in the first three years and then yearly for up to at least five years (6). The European Society for Medical Oncology (ESMO) has different guidelines for rectal (2) and colon cancers (3). For colon cancer, the recommendations are similar to those of ASCO and NCCN: physical examination and CEA testing every six months for three years and then every six to 12 months for years four and five; rectal cancer survivors are only recommended to undergo physical examination every six months for two years. (**Table 2**)

Qualifying Statements
A CBC and other routine blood work, aside from a CEA, are not recommended for routine surveillance.
A Fecal Occult Blood Test (FOBT) is not recommended for routine surveillance.

Abdominal and chest CT scans are recommended annually for three years. A pelvic CT scan is also recommended on the same schedule if the primary tumour was located in the rectum.
Annually for first 3-5years in stage III and in stage II patients with high risk of recurrence.

The ASCO (8) and NCCN (4,5) guidelines recommend performing a ***CT scan of the abdomen*** every year for three years for colon cancer survivors. The ESMO guideline recommendations are similar but with shorter start dates to the intervals: every six to 12 months for the first three years. The Australian (13) guideline recommends a liver CT for CRC survivors but provides no schedule.

ASCO (12) recommends a ***chest CT*** annually for three years. ESMO (3) suggests a chest CT scan every six to 12 months for the first three years in colon cancer survivors who are at higher risk of recurrence and imaging the lungs at one and three years after surgery for rectal cancer survivors. NCCN recommends a pelvic CT scan only for rectal cancer (5). ASCO (12) states that pelvic CT scans can be considered for survivors of rectal cancer. (**Table 2**)

PET Scan
Not indicated as a baseline or for surveillance
FDG-PET plays a pivotal role in the detection of recurrent disease, the assessment of residual masses after treatment, the localization of recurrence in patients with an unexplained rise of serum CEA, and in staging patients before surgical resection of local recurrence and metastatic disease. Correlation between changes in FDG uptake and overall patient survival remains a very worthwhile avenue of research to pursue.

In PET/CT, CT scanner has a second important role beyond diagnostic CT scanning. For PET application, CT is also used for photon attenuation correction and for anatomic localization of PET imaging findings. For these tasks CT images are taken without breath holding, to match PET image acquisition, and typically uses relatively low dose (non diagnostic) CT. Radiation exposure is lower and intravenous contrast is not needed (14).

Qualifying Statement
If local resources and/or patient preference preclude the use of CT, an ultrasound (US) can be substituted for the CT of the abdomen and pelvis and a chest x-ray can be substituted for the chest CT. Every six to 12 months for three years and then yearly for years four and five is a reasonable schedule for these tests.

Key Evidence
The PEBC (6) guideline recommends a liver US every six months for the first three years and then yearly for a total of at least five years. The EMSO guideline (3) suggests that a contrast-enhanced US could substitute for an abdominal CT.

3. Which symptoms and/or signs potentially signify a recurrence of CRC and warrant investigation?

In the expert opinion of the authors, any new and persistent or worsening symptom warrants the consideration of a recurrence, especially:

- Abdominal pain, particularly in the right upper quadrant or flank (liver area).
- Dry cough.
- Vague constitutional symptoms such as:
- Fatigue.
- Nausea.
- Unexplained weight loss.
- Signs and/or symptoms specific to rectal cancer
- Pelvic pain.
- Sciatica.
- Difficulty with urination or defecation.

There are no signs of symptoms specific to colon cancer that would not also apply to rectal cancer.

4. What are the common and/or significant long-term and late effects of CRC treatment?

Common long-term or late effects of treatment for CRC may include the following:
General

- Fatigue
- Distress (e.g., anxiety, depression)

Related to surgery

- Frequent &/or urgent bowel movements or loose bowels—often improves over first few years.
- Gas and/or bloating.
- Incisional hernia.
- Increased risk of bowel obstruction.
- In patients who received ostomy—lifestyle adjustment will be required.

Related to medication

- Peripheral neuropathy (associated with treatment using oxaliplatin).
- “Chemo-brain,” including difficulty with short-term memory and the ability to concentrate.

Related to radiation

- Localized skin changes (i.e., colour, texture, and loss of hair).
- Rectal ulceration and/or bleeding (radiation colitis).
- Anal dysfunction (incontinence).
- Bowel obstruction (from unintended small bowel scarring).
- Infertility.
- Sexuality dysfunction (e.g., vaginal dryness, erectile dysfunction, retrograde ejaculation).
- Second primary cancers in the radiation field (typically about seven years after radiotherapy).
- Bone fracture (e.g., sacral region).

5. On what secondary prevention measures should CRC survivors be counselled?

Despite the lack of high-quality evidence on secondary prevention in CRC survivors, the following counselling goals would be reasonable based on lower levels of evidence and the expert opinion of the authors:

- Maintain an ideal body weight.
- Engage in a physically active lifestyle.
- Eat a healthy diet.

There are insufficient data to make a firm recommendation regarding the role of acetylsalicylic acid (ASA) in the secondary prevention of CRC.

Follow Up in Stage IV

Recommendations are similar to those listed above except that some are indicated more frequently:

- CT scan- chest, abdomen and pelvis
- Every 3-6monthly for 2years
- Every 6-12monthly for total of 5years

Liver metastases are the main cause of death in patients with colorectal cancer. Approximately 20% of patients already have liver metastases at the time of detection of the primary tumor, and another 25% will develop metastatic lesions during the following 4 years (15). Without any treatment, the median survival after the detection of liver metastases is approximately 9 months, depending on the extent of the disease at the time of diagnosis (16). For patients with recurrent disease confined to the liver, resection of the metastases is the treatment of choice and can result in a 5-year survival of more than 40%, depending on the selection criteria for surgery. With the exception of lung metastases, the presence of extrahepatic disease, however, typically precludes surgery as does the involvement of major blood vessels or extensive bilobar liver disease, which would either preclude negative resection margins or would result in inadequate hepatic reserve. A significant number of patients (10–25%) considered suitable for surgical resection of liver metastases appear to have unresectable disease identified during laparotomy (15). Moreover, 60% of patients will develop recurrent tumor after successful hepatic resection within 3 years, indicating that many of the patients must have harbored unrecognized tumor foci either in the liver or in extrahepatic areas at the time of liver resection (15).

Increasing Level of CEA

Physical examination, colonoscopy and CT scan-chest, abdomen and pelvis are indicated. If imaging tests are normal in face of rising CEA, then CT scan scans should be done 3monthly till the lesion is revealed or the levels stabilize. The opinion of NCCN panel on the use of PET scan in case of rising CEA levels in face of normal CT scan was divided. Blind that is, CEA directed laparotomy or laproscopy as well as CEA labeled scintigraphy is not indicated(17).

Figure 1: Selection of clinical practice guidelines, systematic reviews, and meta-analyses from the search results of MEDLINE, EMBASE, and the CDSR.

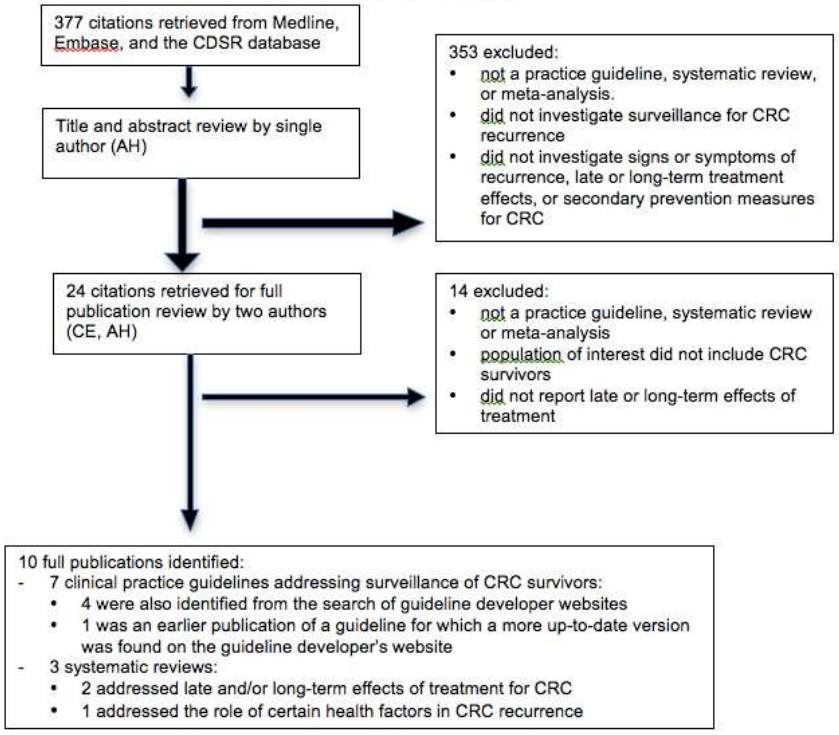

Table 2 Summary of recommendations from identified guidelines

Variable	ASCO (2005) Stage II or III	ACS (2006) Stage I-III	NCCN (2010)* Stage I-III	PEBC (2010) Stage IIb-III (I-III for colonoscopy)	Australia (2005) "curatively resected"	ESMO (2010)* Stage not specified	BSG/ACGBI (2010) Stage not specified	ASCRS/ SPTF (2004) Stage not specified	NZGG (2004) Stage not specified
Physical exam/History	Q 3-6 m first 3 y, Q 6m to 5 y, then at the discretion of the physician		Q 3-6m for 2 y, then Q 6 m for total of 5 y	Q 6 m first 3 y, then yearly for at least 5 y	Q 3-6m for 2 y, then Q 6m-1y thereafter	Rectal: Q 6 m for 2 y Colon: Q3-6m for 3 y then Q6-12m in years 4-5		At least 3 times per year for first 2 years	Q 6 m for 2 y, then yearly for a total of 3-5 y
CEA	Q 3 m for at least 3 y		Q 3-6m for 2 y, then Q 6 m for total of 5 y	Q 6 m x 3y, then yearly for at least 5 y	Q 3-6 m in conjunction with clinical review	Colon: Q3-6 m for 3 y then Q6-12 m at years 4 & 5		At least 3 times per year for first 2 years	
Abdominal imaging	CT: Annually for 3 y		CT: Annually for 3-5y	Ultrasound: Q 6 m first 3 y, then yearly for at least 5 y	CT recommended, no schedule	Colon: CT or contrast enhanced ultrasound, Q 6-12m for first 3 y Rectal, CT: 1 and 3 y after surgery	CT: within 2 y after surgery	Routine use not recommended	
Pelvic CT	Consider for rectal cancer patients		Annually for 3-5y		CT recommended, no schedule				
Chest imaging	CT: Annually for 3 y CXR: not recommended		CT: Annually for 3-5y	CXR: Q 6 m first 3y, then yearly for at least 5 y	CT recommended, no schedule	Rectal : Lung imaging at 1 & 3 y after surgery Colon: CT Q 6-12 m first 3 y		CXR: insufficient evidence to recommend for or against	
Colonoscopy	At 3 y, if normal then Q 5 y	At 1 y, if normal, then at 3 y; again, if normal, at 5 y[A]	At 1 y then as clinically indicated	Yearly as long as polyps are found; if no polyps present, repeat every 3-5 years.	3 to 5 y after the initial operation and then at Q3-5 y intervals	Rectal: Q5yB Colon: at year 1, then Q3-5 y	5 y after surgery then Q5 y intervals	3 y after surgery then Q3 y	3-5 y after surgery then at Q 3-5 y intervals
Recto-sigmoidoscopy	Q 6 m for 5 y for rectal cancer patients who haven't received pelvic radiation				Rectal, anterior resection: Q3-6m then Q 6m-1y thereafter	Rectal: Q 6 m for 2 y			Rectal Q 6 m for 2 y then yearly for at total of 5 y

Notes: ACGBI=Association of Coloproctology for Great Britain and Ireland; ACS=American Cancer Society; ASCO=American Society of Clinical Oncology; ASCRS=American Society of Colon and Rectal Surgeons; BSG=British Society of Gastroenterology; CT=computed tomography; CXR=chest x-ray; ESMO=European Society for Medical Oncology; m=months; NCCN=National Comprehensive Cancer Network; NZGG=New Zealand Guidelines Group; PEBC=Program in Evidence-based Care; Q=every; SPTF=The Standards Practice Task Force; y=year(s).

*Both NCCN and ESMO published two separate guidelines: one on rectal cancer and another on colon cancer.

A Patients who did not have colonoscopy as part of initial diagnostic work-up should have a colonoscopy within 3-6 months of surgery.

B Patients who did not have colonoscopy as part of initial diagnostic work-up should have a colonoscopy within 1 year of surgery.

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Carcinoma Anal Canal

PK Mishra, BG Vageesh

Carcinoma anal canal is an uncommon GI malignancy, constituting 3-5% of all large bowel cancers. More than 70% is constituted by Squamous cell carcinoma (1). Increasing incidence of HIV & HPV infections are the main causes for recent increase in the incidence. Anal canal cancers are highest in HIV positive, homosexual men.

Clear understanding of the anatomical landmarks is very important with respect to classification, staging, treatment planning of anal cancers. Dentate line defines the anatomical canal & anal verge defines the surgical canal. Present AJCC staging (2) has considered anal verge as the cut off line, which differentiates between anal canal tumors & anal margin tumors. Anal margin tumors are mostly treated like skin tumors whereas anal canal tumors need multimodality approach. Bulky tumors crossing these anatomical boundaries with overlap are managed cautiously.

HPV-16 infection, Receptive anal intercourse, HIV infection, Immunosuppression, smoking are found to be the risk factors (3). Several smaller studies demonstrated an approximately 60-fold increase in

the relative risk of anal cancer in HIV-positive patients compared with HIV-negative patients. Kidney transplant recipients have a 100-fold increase in the risk of anogenital cancers. Anal cancers are not caused by benign diseases such as fissure, fistulas, or hemorrhoids even though the diagnosis of benign conditions and anal cancers may be temporally related (4). Similarly, inflammatory conditions such as Crohn's disease and ulcerative colitis are not associated with an increased incidence of anal cancer.

Most common initial symptom is bleeding per rectum. Fresh blood with every stool without any mass or pain leads to most of the misdiagnosis. In 20% of the cases it is totally asymptomatic. Pruritus ani, mucus seepage are nonspecific symptoms. Incontinence, Pelvic pain, rectovaginal/ vesical fistulas are considered to be ominous symptoms.

Detailed clinical history with DRE is almost diagnostic in most of the cases. Chest X-ray, complete colonoscopies with biopsy, to rule out synchronous lesions and CT for proper anatomical delineation are recommended investigations in workup. Addition of PET CT for better functional analysis of metastatic spread is used nowadays.

Anal margin tumors

Condyloma accuminata is a perianal wart caused by HPV-16,18 & most commonly associated with HIV related immunosuppression. Pinkish small warts are found in perianal area along with bleeding, pain & wetness. Giant form is called Buschke Lowenstein tumor. Podophyllin, Dichloraceteic acid are used in the treatment .But Imiquimod 5% cream for local application thrice weekly is most recommended.

Anal Intraepithelial Neoplasia (AIN) is precursor to squamous cell carcinoma. It is classified in to 3 grades: AIN I, AIN II, and AIN III, which indicate low-, moderate-, and high-grade dysplasia respectively. LSIL replaces AIN I and HSIL replaces AIN II, AIN III, CIS and Bowen disease. LSIL is believed to have a low malignant potential and may be followed by surveillance examination at 6-month intervals. HSIL carries a more significant risk of malignant transformation and treatment is often pursued, although observation with close surveillance is an acceptable strategy(5).

Bowens disease is a squamous cell carcinoma in situ. Most commonly presents with localized confluent lesions & are amenable for wide local excision . Local application of 5 FU is also frequently used. Squamous cell carcinomas of anal margin behave like skin cancers & most of the cases need local excision without radiation. Even few studies have shown long term side effects of RT in case of SCC of anal margin (6). Aggressive disease, recurrent disease, patients refusing for APR in a rapidly progressive disorder are the indications for RT in anal margin SCC. Pagets disease is an intraepithelial anal adenocarcinoma. More than 70% of the cases are associated with underlying malignancy (7). Presence of PAS positive paget cells on histology are classical feature of this condition.

Wide local excision is offered in selected cases. APR is done in proven malignancies with supradentate extension & CTRT is offered in epidermoid carcinomas. Basal cell carcinomas are rare cancers with peripheral palisading as the classical histological feature. Wide local excision is done in most cases with APR reserved for advanced diseases. As in skin, BCC are known for recurrence in this region also.

Anal canal tumors

Conglomeration of various cell types is the peculiarity of this region. At anal transition zone we have basaloid, cloacogenic, squamous & mucoepidermoid cells. Malignancies arising in this region from any of the following cells have same presentation, similar treatment response & prognosis. At presentation, 30% of tumors are T1 disease & 70% are T2 & more advanced disorders. 20% of the tumors are node positive & 5% are distal metastatic disorders (8). In AJCC system depth of the tumor is considered for T staging & holds the prognostic significance.

Prior to Nigro's report in 1974 of the efficacy of combined radiation and chemotherapy, the standard of care for anal cancers was the abdominoperineal resection. The overall cure rate for resectable anal

cancers with APR alone is about 70%. Today, surgical therapy for anal cancers has been relegated to salvage therapy in almost all cases(9).

Approximately 30% of patients have persistent or recurrent disease after chemoradiation for anal SCC. APR is recommended for persistent or recurrent disease, with achievable 5-year survival rates between 24% and 58%(10). Radiation therapy alone is highly effective at obtaining local control with local eradication of tumor and cure in 70 to 90% of patients. The probability of cure is greatly reduced in patients with larger tumors and positive lymph nodes. Tumor eradication is achieved in patients who receive at least 54 Gy of external beam radiation. Chemoradiation is the standard of treatment in Ca anal canal at present (11).5-FU (1000 mg/m2/d) given as a continuous infusion for 4 days, mitomycin C (15 mg/m2) as a single intravenous bolus injection, and 3000 cGy (200 cGy/d) of external beam radiation to the pelvis.5-FU was repeated on days 20 to 31 and mitomycin C on day 29.
UKCCR, EORTC and RTOG are the main RCTs comparing CRT in different combinations. UKCCR & EORTC trials have shown that with the above mentioned CRT there is a reduction in local failures (18% and 46%, respectively), lower likelihood of recurrence, lower likelihood of eventual colostomy & there is no difference in overall survival. CRT is better than RT alone (ACT 1 & EORTC). CRT needs Mitomycin C (MMC) (RTOG 8704). Neoadjuvent Cisplatin has no added advantage(ACCORD-3 & RTOG 98-11) than CRT.

Overall incidence of clinically positive inguinal lymph nodes is 10–20%. 25% of lymph node positive patients have bilateral involvement. Formal prophylactic node dissection is unnecessary. Biological targeted therapies are under evaluation for the treatment of Ca anal canal.

According to ESMO guidelines, Minimum of CT of Chest, Abdomen and Pelvis is required for staging of disease. MRI is currently the modality of choice to assess locoregional disease (12). Local excision can be considered for small well-differentiated carcinomas of the anal margin (T1 N0) i.e. <2 cm in diameter, without evidence of nodal spread (level of evidence III) and no sphincter involvement.

Locally persistent progressive disease should be considered for surgical salvage with abdomino-perineal excision. Biopsy is mandatory and restaging for metastatic disease is recommended before resorting to surgery.

Overall 5-year survival - 58%. For Stage 1 it is 69.5%, for Stage II -59%, Stage III - 40.6% .Stage IV-18.7%. TNM stage, size of tumor, Location of tumor, presence of ulceration are considered to be the prognostic factors.

Anorectal melanoma is a rare condition & needs wide local excision for localized anorectal melanoma & APR for bulky tumors invading the sphincter mechanism (13). APR is recommended for localized disease associated with underlying carcinoma. Kaposi's sarcoma & Verrucous carcinoma are few rare varieties of anal carcinoma.

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Surgeries for Breast Cancer

P. N Agarwal, Varun Jain

HISTORICAL ASPECT

Pre- Halsted era

The ancient Egyptians, according to the Edwin Smith papyrus (3000 B.C), did not believe that breast cancer could be cured.[1] The writings of Hippocrates include sparse commentary on breast cancer in particular. Hippocrates described a malignant tumor as having a dismal prognosis, beginning as a small lesion, and growing in size to eventually cause death. He cautioned that the smaller tumors should be left alone because, if treated, the patient dies sooner.[1,2] Roman physicians in the first century aggressively removed breast tumors, sometimes excising the pectoralis muscles along with the breast.[2] Galen, the Roman physician (120 –200 AD), was the first to promote clear margins and the removal of "crab-like" tumor extensions, discouraging the use of cautery because of potential damage to surrounding structures.[1,3] Albucasis, the tenth century Arabian surgeon, used cautery to surgically treat breast cancer, but doubted the disease could ever be cured.[1,2] Ambroise Pare´ (1510 –1590) managed large ulcerating cancers with salves, but excised the smaller breast cancers, seeking clear margins. Pare´ was among the first to recognize the role of the axillary nodes in the spread of breast cancer.[1,2] Andreas Vesalius (1514 –1564) described the detailed anatomy of the breast, allowing surgeons to place ligatures strategically to control bleeding and enhance dissection.[4] Gerard Tabor's mastectomy instrument, described in 1721, facilitated rapid extirpation of the breast.[1] Charles Hewitt Moore (1821–1870) of London published his treatise condemning inadequate operations for cancer in 1867. He initially recommended excising only clinically enlarged axillary nodes, but then realized that involved nodes can be unrecognized, so he began performing complete axillary lymphadenectomy.

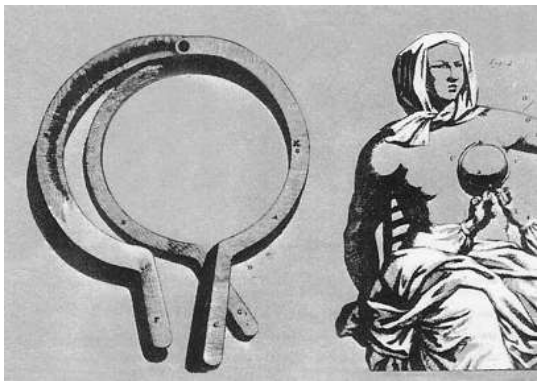
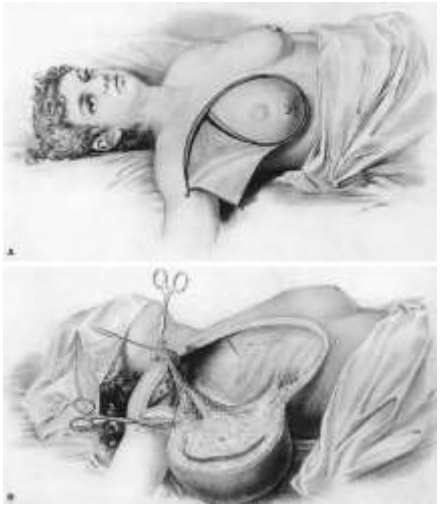


Illustration of Tabor's mastectomy instrument described in 1721

Halsted era- Radical Mastectomy

William Stuart Halsted received his medical degree from Columbia College of Physicians and Surgeons, graduating first in his class in 1877. He was the first to remove both pectoralis muscles for advanced tumor, and he noted better results in those patients than in patients with less extensive disease, who did not have the muscles removed.



Halsted's classic operation—the en bloc removal of the entire breast, regional lymphatics, and pectoralis muscles—he applied the philosophy and techniques of Moore, Kuster, Volkmann, and Heidenhain. Halsted first performed his radical mastectomy in 1882, and he published his classic work in 1894 in the Johns Hopkins Hospital Reports.[5]

This surgery was based on the principle of centrifugal or contiguous spread of disease where in the tumour cells spread form the breast primary in a sequential manner from one lymph node station to the next and there on to systemic spread. 5-year

cure rate after radical mastectomy was 40%; excellent survival considering that three-fourths of his patients had axillary node involvement.

Halsted's Radical Mastectomy

Jerome Urban of Memorial Hospital in New York introduced the extended radical mastectomy in 1951. This added en bloc resection of the chest wall and internal mammary nodes to the standard Halsted mastectomy in patients with central and medial breast lesions. Owen Wangensteen, at Minnesota in 1956, included the internal mammary, supraclavicular, and mediastinal nodes in his super-radical mastectomy. These however, had more morbidity and mortality and did not show any survival advantage and therefore, were soon abandoned.

Patey's era- Modified Radical Mastectomy

The impetus to perform an operation less radical than the Halsted mastectomy began in the early 1930s when D. H. Patey of the Middlesex Hospital in London introduced what came to be known as the "Patey Operation," but termed "modified radical" by Patey. He spared the pectoralis major muscle, contending that routine removal of the pectoralis major did not add to the value of the mastectomy, and resulted in significant intraoperative blood loss and cosmetic deformity.[6] Removal of the pectoralis minor allowed access to and clearance of axillary lymph node levels I to III (Patey modification). Today the modification is limited to severance of the origin of the pectoralis minor muscle at the coracoid process of the scapula. Subsequent to the description of the Patey modification, Madden advocated a modified RM that preserved both the pectoralis major and minor muscles even though this approach prevented complete dissection of the apical (level III) axillary lymph nodes. George Crile, Jr., of the Cleveland Clinic, well ahead of his time, was an early proponent of breast conservation.

The Mayo Clinic reported 12,641 operations for breast cancer performed from 1910 to 1964.[7] Ninety percent of the women had the standard Halsted operation, and 10% had a modified radical mastectomy; half of each group received radiation. This retrospective study showed that positive axillary nodes greatly influenced survival, but there was no difference in cure rate at 5 or 10 years when the axillary nodes were negative.

Fischer era

Dr Rudolph Noer initiated the National Surgical and Adjuvant Breast Project (NSABP) in 1957. Dr Bernard Fisher of the University of Pittsburgh, who has remained the principal protocol coordinator, soon succeeded him. Various operations, adjuvant radiation, chemotherapy, and hormonal treatment have been studied in a prospective, randomized manner. The success of less extensive surgery for breast cancer has now been established after 45 years of well-designed studies.

The NSABP B-04 protocol was conducted from 1971 to 1974 with 34 participating institutions from the United States and Canada. The 10-year results, published in 1985, established Halsted's radical mastectomy as an operation of historical interest only.[8]

The NSAPB B-06 trial was initiated in 1976 and evaluated breast conservation in Stage I/II breast cancer. This study randomized 1843 patients with cancers less than 4 cm into 3 arms: total mastectomy, segmental mastectomy, and segmental mastectomy with radiation. All patients received axillary node dissection, and those with positive nodes received adjuvant chemotherapy. The results of this study at 5 and 8 years showed no difference in disease-free survival among the 3 groups.[9,10] There was an increase in local recurrence in those patients in the segmentectomy group without radiation. This investigation supported the use of segmentectomy with radiation in patients with Stage I/II breast cancer, and it concluded that irradiation reduces the incidence of local recurrence after segmentectomy.

The NIH Consensus Conference of 1990 recommended breast conservation for patients with Stage I and II breast cancer. It also recommended routine Level I and II axillary dissection for staging and for prevention of axillary recurrence.[11]

Breast conserving surgery

Lumpectomy or wide local excision (partial or segmental mastectomy) is defined as complete surgical resection of a primary tumor with a goal of achieving widely negative margins (ideally 1 cm). Aim is to achieve long-term local disease control with minimum local morbidity.

Indications

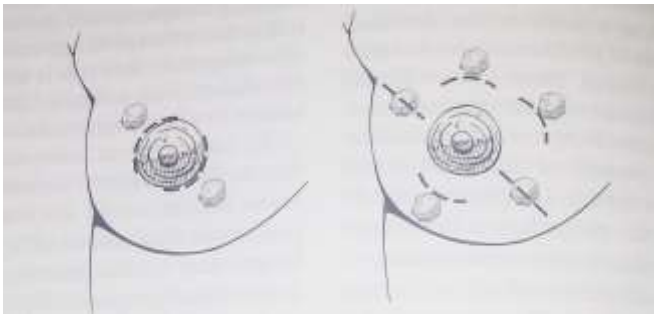
- T1, T2 (<4cm), N0, N1, M0
- T2 > 4cm in large breasts
- Single clinical and mammographic lesion

Absolute contraindications include the following:

- T4, N2, M1 (some localized T4 disease and some patients with limited metastatic disease may be suitable for breast- conserving surgery)
- Clinically evident multifocal or multicentric disease
- Patients who prefer mastectomy
- History of previous radiation therapy to the area of treatment
- Inability to undergo radiation therapy
- First or second trimester of pregnancy
- Persistent positive margins after previous attempts at conservation

Relative contraindications include the following:

- Small breast size
- Large or central tumours in small breasts
- Collagen vascular disease
- Women with a strong family history of breast cancer or BRCA1 and BRCA2 mutation carriers



Incisions for BCS. Periareolar incision for centrally placed lesions and curvilinear incision for peripherally located lesions. Radial incision for upper- outer and lower- inner quadrants. (Mastery of Surgery, 6th Ed.)

In centres that specialize in breast cancer treatment, approximately 75 percent of women with early stage breast cancer are candidates for BCT. In 25 to 50 percent of women, there are medical, cosmetic and/or social and emotional reasons for having a mastectomy rather than BCT. Survival outcomes are the same whether BCT or mastectomy is performed.

There is evidence of significant variation in margin definitions, positive margin rates, and re-excision lumpectomy rates (RELR) in patients undergoing BCS.[12,13] Current NCCN guidelines for DCIS state, margins less than 1 mm are considered inadequate.[14]

After BCS, all patients are required to undergo whole breast radiation along with boost radiotherapy to the tumour bed, followed by systemic therapy as per standard protocol.

Mastectomy

Total Mastectomy- involves complete removal of all breast tissue from the subclavius superiorly, the sternal border medially, inferiorly till the caudal extention of the breast, about 3- 4cm inferior to infra-mammary fold, and the anterior margin of latissimus dorsi laterally, with en bloc resection of the pectoralis major fascia.

Indications for total mastectomy include

- Risk-reducing mastectomy
- Local recurrence in a previously treated breast cancer
- Palliative procedure in metastatic breast cancer
- Malignant phyllodes tumor

The following variants are performed:

- Modified radical mastectomy – A total mastectomy with axillary lymph node dissection (ALND)
- Radical mastectomy – A total mastectomy plus en bloc resection of the pectoralis muscles, and ALND (complete Level I-III axillary LN dissection)
- Extended radical mastectomy – A radical mastectomy with resection of the internal mammary lymph nodes

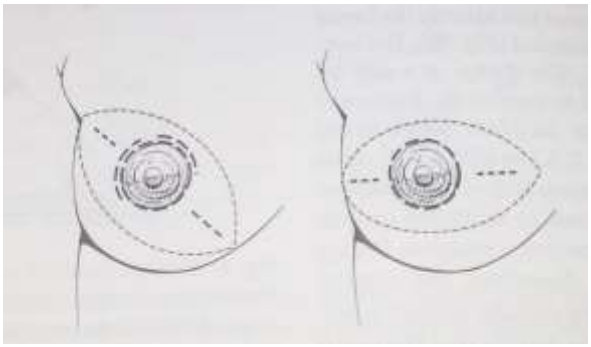
The modified radical mastectomy has various modifications

Patey modification- removes the pectoralis minor muscle, allowing complete dissection of apical (Level III) axillary lymph nodes

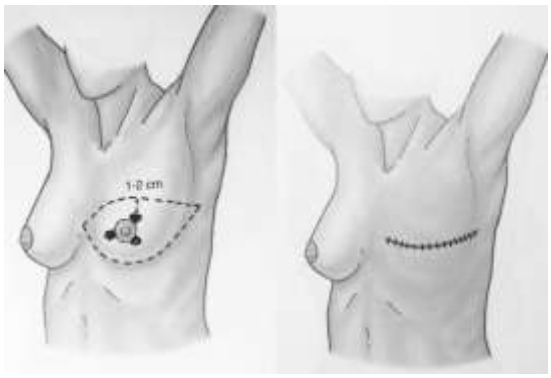
Scanlon- Pectoralis minor is divided but not removed (allows level III dissection)

Auchincloss- Pectoralis minor is only retracted (allows only Level I and Level II dissection)

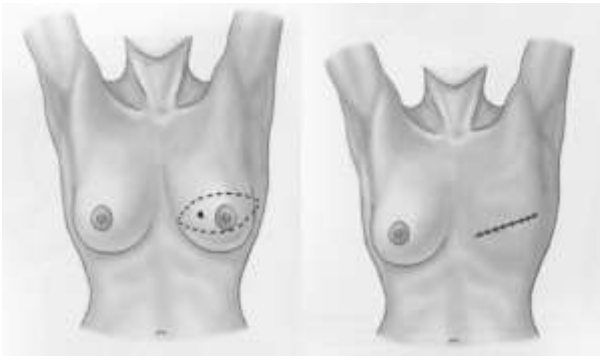
Various incisions are available for Mastectomies



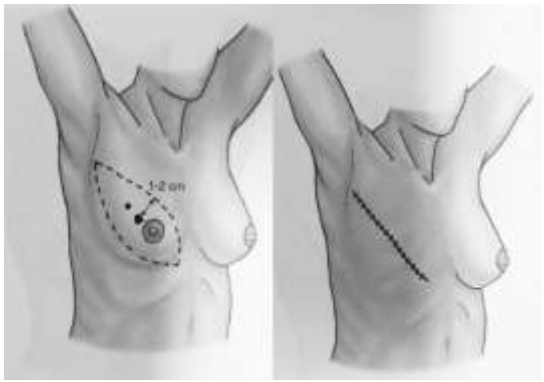
Incisions for standard total mastectomy. Oblique or transversely oriented elliptical incisions. (Mastery of Surgery, 6th Ed.)



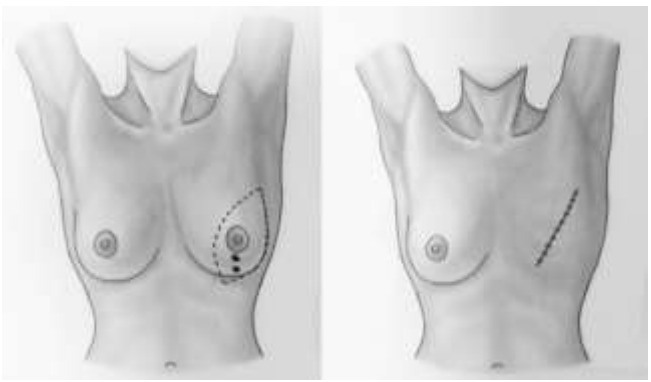
Classic Stewart elliptical incision (Mastery of Surgery, 6th Ed.)



Oblique modified Stewart (Mastery of Surgery, 6th Ed.)



Classic Orr oblique incision

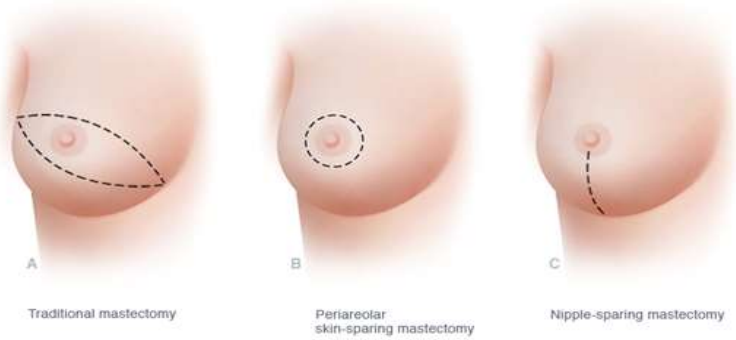


Variation of Orr incision

Complications after mastectomy include the following:

- Wound infection
- Seroma
- Mastectomy skin flap necrosis
- Hematoma
- Chronic pain
- Incisional dog ears
- Lymphedema (if axillary dissection is done)
- Fibrosis
- Risk of local recurrence

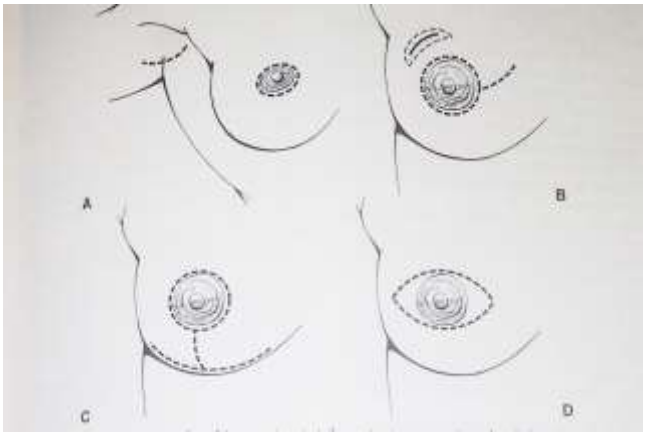
Other Variations of Mastectomy



Comparison of skin incisions

Two modern variations of the total mastectomy include the skin-sparing total mastectomy (SSM) and the nipple-sparing total mastectomy (NSM). These operations refer to surgical approaches designed for patients who elect to have immediate reconstruction. It should be noted however, that NSM can only be done in peripherally located lesions.

Both SSM and NSM are minimally invasive surgical approaches that are technically more difficult and, thus, more time-consuming than traditional mastectomy. SSM and NSM result in preservation of the patient's skin envelope and maintain the position of the inframammary fold. However, both SSM and NSM are intended to be complete total mastectomies with the same extent of resection as a traditional total mastectomy.



Incisions for skin sparing mastectomies. A. Periareolar, B. Tennis racquet, C. Reduction mammoplasty, D. Modified elliptical.
Axillary dissection may be done through separate skin incisions. (Mastery of Surgery, 6th Ed.)

These operations may not be appropriate for cancers near the skin or nipple. Additionally, SSM or NSM are not appropriate for locally advanced or inflammatory breast cancer. Multiple retrospective single-institution studies have reported excellent results with SSM and NSM. No randomized clinical trials have compared survival results for SSM, NSM, and total mastectomy. One study analyzed breast cancer recurrence data on patients who had undergone mastectomy with immediate

reconstruction versus those who had not undergone reconstruction after mastectomy and concluded that neither incidence nor time to detection of recurrent disease was impacted by reconstruction.[15]

However, most surgical oncologists accept that as long as SSM and total mastectomy are performed carefully and patients are selected carefully, these are reasonable oncologic choices for prophylactic mastectomy and for the treatment of selected early stage breast cancers.[16]

Management of Axilla

Axillary Lymph Node Dissection (ALND)
ALND is a complete en bloc removal of the level I and level II lymph nodes; the level III nodes are not removed routinely now, unless suspicious or palpable adenopathy is present. All nodal tissue defined by the borders of the axillary vein superiorly, the latissimus dorsi laterally, the medial border of the pectoralis minor medially, and the subscapularis posteriorly is removed.

Care is taken to preserve the long thoracic and thoracodorsal nerves along their course through the axilla. Injury to the long thoracic nerve results in a winged scapula, whereas injury to the thoracodorsal nerve compromises internal rotation and abduction of the arm beyond 90°.

The median and lateral pectoral nerves may also be injured during axillary lymph node dissection. The intercostobrachial nerves run directly through the resection specimen and are typically sacrificed, resulting in a predictable pattern of cutaneous numbness in the inner arm region for most patients after this procedure.

Axillary lymph node dissection carries a high rate of surgical morbidity, including the following:
- Lymphedema (rates of about 25%)
- Shoulder dysfunction
- Wound infection
- Seroma
- Nerve damage
- Numbness
- Chronic pain
- Brachial plexus injury (rare)

Axillary lymph node dissection was previously considered the standard of care for all patients diagnosed with invasive breast cancer, however, with the option of sentinel lymph node biopsy there is a shift towards a conservative approach wherever possible.

Sentinel Lymph Node Biopsy

Sentinel lymph node (SLN) biopsy is a minimally invasive procedure designed to stage the axilla in breast cancer patients who have clinically negative nodes. Sentinel nodes are the first node or first group of nodes that drain from the breast to the axilla.

Sentinel node biopsy is currently the standard of care for management of the axilla in early breast cancer.[17] Proponents cite the importance of the sentinel node biopsy in preventing unnecessary staging lymphadenectomy in the substantial number of patients who are node-negative. Armando Giuliano, at the John Wayne Cancer Institute, had championed sentinel node biopsy in breast cancer, using 1% isosulfan blue dye to locate the sentinel node(s) in the axillary nodal basin. Veronesi in Milan, in 1997, applied lymphoscintigraphy and gamma-probe guided biopsy in operable breast cancer patients with clinically negative nodes, correctly predicting axillary nodal status in 97% of cases.

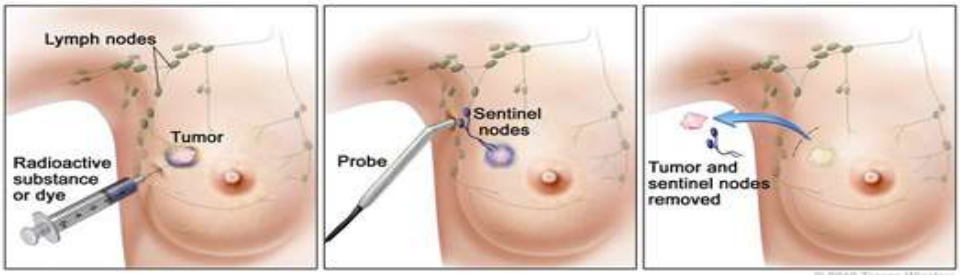
There are two methods for performing SLNB. Methylene blue dye method and a Radioactive isotope method. Gold standard is the combined method.

1) Radio- isotope method
At least 1 hour before surgery dermal injection of radiocolloid is given in the skin overlying the tumour in 5 locations. 0.5 mCi (filtered 0.2 micron) Tc sulphur colloid in a volume of 0.5cc is used. Sub-

areolar injection may also be given. During surgery, a gamma probe is placed in the axilla, to localize the radioactive node.

2) Dye Method

Two blue dyes are available, methylene blue and isosulphan blue. 3-5 ml of either of the blue dyes is injected either peri- tumorally or sub- areolar and then breast massage is given for 5 to 10 minutes. After this painting and draping is done. Incision is made in the axilla and stained node is identified.



SLN biopsy has become the preferred SLN technique for axillary staging, because it offers accuracy equivalent to that of axillary lymph node dissection with less morbidity.[17]

The American College of Breast Surgeons (ACBS) states the following:

- SLN biopsy is suitable for virtually all patients with clinically node-negative T1-2 invasive breast cancers
- Limited data are available regarding the suitability of SLN biopsy for patients with T3 cancers, multifocal/multicentric disease, prior radiation therapy, or prior breast/axillary surgery
- SLN biopsy is also indicated in patients with ductal carcinoma in situ (DCIS) in whom mastectomy is required or invasive disease is suspected
- The role of SLN biopsy in patients who have had neoadjuvant therapy remains controversial and is currently under study.
- There is no role for SLN biopsy in inflammatory breast cancer.

Postoperative care

Immediate postoperative care involves the following:

- Assessment for appropriate wound healing
- Evaluation and treatment of postoperative complications, such as seroma, wound infection, bleeding, and nerve damage. (Role of suction drain post operatively, is also under study).
- Follow-up of the pathologic specimen and decision on adjuvant therapy.
- Encouragement of early patient mobility and range-of-motion exercises

Recommendations for longer-term follow-up are as follows:

- Baseline postoperative mammography of both breasts or of the remaining breast at 6 months
- Clinical assessment every 4 months during the first 2 years, every 6 months up to the fifth year, and then annually for the remainder of the patient's lifetime
- Annual mammography and chest radiography
- No further workup except as indicated by the development of suggestive symptoms such as bone pain, headache, or abnormal findings on annual routine laboratory chemistry panels

Breast reconstruction

Oncoplastic surgery is a rapidly advancing field that uses local tissue rearrangement to reconstruct a partial mastectomy defect. Options include fasciocutaneous local tissue advancement flaps, breast parenchymal local flaps, or myocutaneous flaps. The selection of aesthetically appropriate incisions also impacts the overall cosmetic result after lumpectomy.

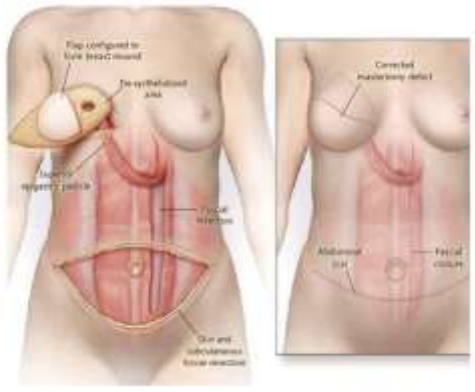
Silverstein and Lagios reported a variety of options for oncoplastic approaches to breast conservation. Kronowitz et al reported that partial mastectomy reconstruction produces superior aesthetic results and lower complication rates when performed before radiation therapy.[18]

Breast reconstruction after mastectomy may be performed in the immediate or the delayed setting. Most patients undergoing mastectomy for prophylaxis or early stage breast cancer are candidates for reconstruction.

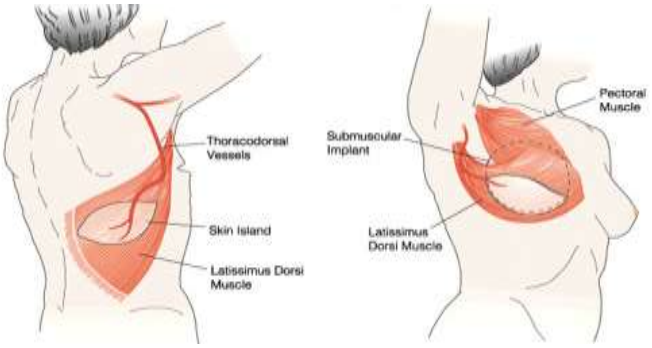
Immediate reconstruction, when feasible, generally provides superior cosmetic results, because a skin-sparing total mastectomy (SSM) or nipple-sparing total mastectomy (NSM) may be offered to selected patients, resulting in preservation of the native skin envelope and inframammary crease. However, when postmastectomy radiation is likely or a reconstructive surgeon is unavailable, delayed reconstruction following all adjuvant therapies may be recommended.

Postmastectomy reconstruction Options are as follows:

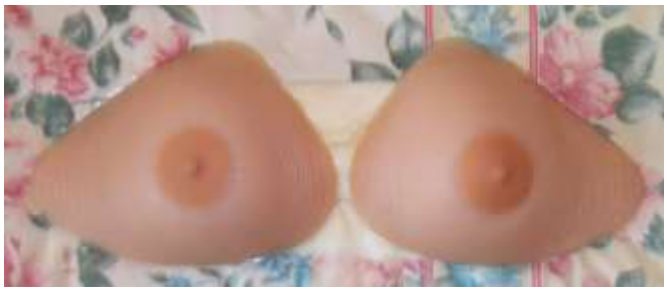
- Split skin graft- for primary coverage of wound/ defect
- Implant-based methods – Tissue Expanders and saline or silicone implants
- Myocutaneous Flaps –
    A) Transverse rectus abdominis myocutaneous (TRAM) flap. Conventional TRAM flap is based on musculo- cutaneous perforating branches from deep superior epigastric artery and vein. Free TRAM flaps utilize the deep inferior epigastric artery and vein.
    B) Lattissimus dorsi (LD) flap is based on thoracodorsal vascular bundle.
    C) Other options for free flaps can be based on, Superior Gluteal Artery Perforator (SGAP), Inferior Gluteal Artery Perforator (IGAP), Deep Inferior Epigastric Artery Perforator (DIEP), Superficial Inferior Epigastric Artery (SIEA) among others.
- A combination of the 2 methods



TRAM flap reconstruction



LD flap reconstruction



Breast prosthesis used after mastectomy

Custom nipple prostheses

The following complications may be encountered:

- Infected or ruptured prosthetic implant
- Capsular contracture
- Flap necrosis or loss
- Fat necrosis
- Asymmetry
- Scarring

Patients and physicians should have realistic expectations for breast reconstruction. Although excellent results may be achieved, often multiple operations are required for revisions, symmetry procedures, and nipple reconstruction.

Over the years surgery for breast cancer has seen an endless transformation which continues still and will in the future as well. The eventual goal has always been to minimize patient morbidity and

mortality and yet, respect oncologic principles. Procedures are being tailored to appropriately treat the disease of the patient, and provide the satisfaction of the best possible cosmetic outcome.

With a multitude of treatment options available, the patient and family members should be made to participate in the decision making process and treatment. All available options must be discussed at length, informing about all pros and cons of the various options and then the patient as well as the family members should be allowed to make an informed decision regarding the management of this disease.

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Chest Trauma

Harinder Singh Bedi

Definition

Trauma to the chest is usually divided into blunt and penetrating injury. Proper emergency care, team work and resuscitation are integral parts of the management of these patients, who may have airway obstruction, life-threatening hemorrhage, and severe associated injuries.

Thoracic injury is directly responsible for 25% of trauma deaths and contributes to death in another 25%. Most of the former occurs at the place of injury and is due to disruption of the heart, great vessels or tracheo-bronchial tree. Most chest injuries esp. blunt are frequently associated with injuries to the liver/spleen, pelvic fractures, and CNC injuries – hence the importance of team work.

Blunt Thoracic Trauma

1. Chest Wall Injuries

- Rib fracture is the most common thoracic injury. Analgesia is the mainstay of therapy for uncomplicated rib fractures. Strapping should be avoided as it leads to atelectasis .
- Significant intrathoracic injury may be present without rib fracture in children due to rib cage elasticity
- Narcotics and intercostal nerve blocks are sufficient for simple rib fractures to control pain
- Patients with significant flail chest interfering with ventilation should be supported with mechanical ventilation for several days to regain chest wall stability. Rarely a surgical fixation of the flail segments may be done eg if the patient is undergoing thoracotomy for a hemothorax
- Consider tracheostomy for prolonged intubation to minimize laryngeal injury and facilitate pulmonary care
- First rib fracture indicates significant force, and ultrasound / CT angiography is indicated if the patient also has brachial plexus deficit, absent radial pulse, pulsating supraclavicular mass, or widened mediastinum

2. Pulmonary Injuries:

- *Pulmonary contusion* probably occurs to a varying degree in all thoracic injuries and is a major component of flail chest. They may be missed at the initial X Ray and be evident only at 24-36 hours. Likewise the patient may be stable at presentation only to deteriorate rapidly after 18- 36 hours. Significant hypoventilation and shunting from contusion requires judicious fluid management and ventilatory support, if indicated.
- Partial, complete, and tension *pneumothorax* should all be managed promptly with chest tube insertion
- *Open pneumothorax* (sucking chest wound): Immediate treatment is to seal the defect with petrolatum gauze. Tube thoracostomy can then be done to remove air and blood and allow the lung to re-expand. The defect can then be repaired in the OR
- Pulmonary *lacerations* can occur in blunt trauma due to rapid deceleration and shearing stress. They can present as hydro-pneumothorax and generally seal after tube thoracostomy. A continuous massive air leak mandates operative intervention and repair of the laceration with sutures or staples or rarely resection
- *Subcutaneous emphysema* should prompt investigation for pneumothorax but is not in itself an indication for chest tube placement. If massive – it requires decompression by multiple incisions on the chest wall up to the muscle layer.
- Multiple *rib fracture* is not in itself an indication for chest tube placement unless pneumothorax is present. It is a common false myth that all multiple rib fractures without pneumothorax needing GA (eg for associated abdominal injury needing laparotomy) require a chest tube.
- *Hemothorax* should be managed with early chest tube drainage to prevent clot formation and incomplete evacuation. Most hemothorax after blunt injury are due to minor lacerations of chest wall muscle/ vessel/ lung. Bleeding is usually moderate and likely to stop when the pleural space is drained and the lung allowed to re-expand. If bleeding continues at a moderate pace (< 100 ml / hr) in a stable patient – coagulation defects, hypothermia, acidosis, hypocalcemia etc should be looked for and corrected. Massive bleed (>1500ml stat and > 250 ml/hr) esp in an unstable patient mandates an immediate operative intervention
- A clotted hemothorax should be evacuated early by thoracotomy to improve pulmonary function and prevent late fibrothorax

3. Tracheal/Bronchial Injuries

- Most tracheal injuries are cervical and range from crush injuries to compete tracheal separation
- If endotracheal intubation is not possible, a surgical airway should be obtained
- Primary repair of tracheal lacerations or separation should be performed, if possible
- Blunt trauma typically causes a circumferential laceration of either main bronchus with complete separation
- Only 50% of patients will have a pneumothorax with this injury, and hemothorax is uncommon
- Only 1/3 of patients are diagnosed in the first 24 hours, and only 1/2 within the first month
- Early repair is the preferred treatment if the diagnosis is made, and requires thoracotomy
- Late strictures from incomplete tears or parenchymal isolation from complete tears can be repaired with bronchoplastic procedures, but may require pulmonary resection

4. Cardiac/Great Vessel Injuries

- Myocardial contusion is the most common injury and is suspected by the presence of EKG changes and serial enzyme elevations in minor damage and pump failure in major damage
- Coronary artery injury can result in thrombosis and myocardial infarction
- Atrial or ventricular rupture is usually fatal, although the pericardium may restrict bleeding long enough to allow survival to the ER. Generally the low pressure right heart chambers can rupture and be contained by an intact pericardium to produce tamponade. An additional torn pericardium will prevent containment and can prove fatal.
- The patient should be monitored in the ICU
- Echocardiography and angiography are indicated for tamponade and post-injury murmurs, which suggest valvular insufficiency or septal defect
- Aortic rupture is also usually fatal, but can result in formation of a false aneurysm, typically at the aortic isthmus
- Patients with a widened mediastinum on CXR should have prompt CT aortography, which will demonstrate an intimal tear / rupture
- Surgical repair should be done promptly, as fatal hemorrhage can occur at any time
- Techniques include LA-FA bypass, proximal aorta-distal aorta shunting, and cross-clamping without cardiopulmonary bypass. Recently selected cases have been managed with endovascular covered stent grafting .

5. Diaphragm Rupture

- Most lacerations occur on the left hemidiaphragm and result from automobile accidents
- Usually, the stomach herniates and undergoes volvulus, massively dilates, and causes left lung collapse and mediastinal shift to the right
- Gastric distension can also result in perforation and should be prevented by NG tube placement
- Splenic and liver injury is also common in this setting
- The diaphragm can be repaired either through the chest or abdomen, and all tears should be closed in double-layer fashion

Penetrating Thoracic Trauma

Comment: Knowledge of the type of weapon in gunshot wounds is useful, as unbalanced or hollow point ammunition can cause extensive internal destruction despite small entrance wounds. In addition, such missiles can fragment and embolize.

It is important to remember that any penetrating injury to the fourth interspace or below may well have passed through the diaphragm, and attention given to possible intra-abdominal injury.

1. Chest Wall Injuries

- Laceration of intercostal or internal mammary arteries can be life-threatening and require operative intervention based on chest tube output
- The pulmonary vessels are rarely the source of major bleeding unless a hilar vessel is injured
- High-velocity missiles and shotgun wounds can produce extensive open wounds requiring immediate occlusion and intubation, followed by operative repair

2. Pulmonary Injuries

- Most penetrating wounds only require chest tube insertion and lung expansion
- Parenchymal injuries requiring operation can usually be oversewn or stapled without difficulty
- Bronchial or pulmonary artery injury can require resection
- A large vascular clamp placed across the lung hilum facilitates exploration and vessel repair

3. Base of Neck Injuries

- The close proximity of major structures make injury highly probable
- This can be assessed by angiography, contrast swallow, endoscopy, or surgical exploration
- The surgical approach will vary, but median sternotomy with lateral or superior extension provides the widest exposure
- Avoid prosthetic grafts for vascular repair if the trachea or esophagus are also injured
- Cardiopulmonary bypass may be required if the aorta must be cross-clamped

4. Cardiac/Great Vessel Injuries

- The right ventricle is most commonly injured, followed by the left ventricle
- Ventricular septal defect is the most commonly intra-cardiac injury
- Most patients do not reach the hospital, as the injury to the pericardium leads to exsanguination instead of tamponade
- Hypotension that does not respond to rapid volume replacement suggests significant injury
- Echocardiography should be done immediately
- Subxiphoid pericardiocentesis is useful and a drain should be left in place
- Subxiphoid pericardial window is preferred for tamponade, however, and should be performed in the operating room, as the patient may rapidly exsanguinate if bleeding continues – this (active intra-pericardial bleed) will require sternotomy and control of the bleeding site.
- Emergency room thoracotomy is seldom indicated, being reserved for moribund patients or rapid deterioration without time to transfer to the OR
- Median sternotomy is the preferred approach
- Right ventricular rents – these can be repaired with pledgetted nonabsorbable horizontal mattress sutures.
- Oversew atrial or aortic injuries
- Coronary artery division should be managed by ligation and bypass grafting on cardiopulmonary bypass
- Obvious septal defects or gross valvular insufficiency causing hemodynamic instability should be repaired; otherwise, the injury should be more adequately studied with cardiac catheterization and operated electively

5. Tracheal/Bronchial Injuries

- Tracheal injury is suggested by pneumothorax, pneumomediastinum, subcutaneous emphysema, hemoptysis, and airway obstruction
- An anterior collar incision is the best approach
- Median sternotomy may be required for associated vascular injury or intrathoracic tracheal laceration
- Avoid tracheostomy if possible when a vascular repair is in proximity

Esophageal Injuries

- Blunt injury is rare; the most common cause is endoscopic perforation, followed by penetrating injuries
- Mediastinitis is a lethal complication and early surgical intervention is recommended
- Cervical esophageal injury should be approached through a lateral neck incision and thoracic injuries via thoracotomy
- If the tissue is not extensively damaged, primary repair with drainage is appropriate; otherwise, the wound is left open
- Postemetic rupture (Boerhaave's syndrome) presents with pain, fever, and shock; death can occur within 24-48 hours
- The diagnosis is suggested by cervical and mediastinal air, widened mediastinum, and pleural effusion
- The esophagus should be closed in two layers, the mediastinum widely opened, and the area drained into the pleural space via thoracotomy

Complications of Thoracic Trauma

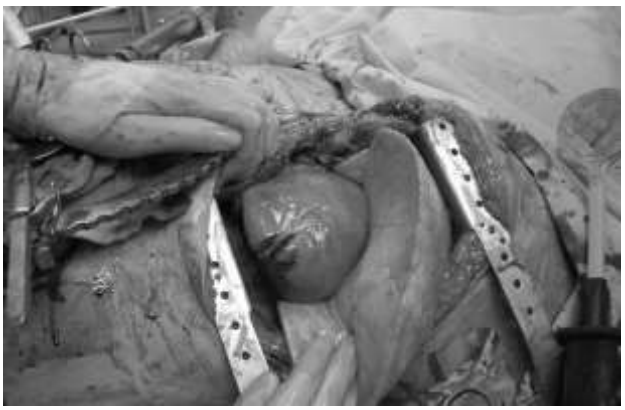
- ARDS follows many types of injuries, but is particularly common in thoracic trauma
- It typically begins a few hours after injury and progresses rapidly
- Ventilatory support with PEEP and high FIO2 is the standard of care
- Failure of ARDS to improve after 4-6 days is associated with a high incidence of death
- Arrhythmias are common in this patient population, particularly atrial fibrillation, which can be treated with standard measures
- Ventricular arrhythmias suggest myocardial injury or infarction and should be investigated
- Many patients will require tracheostomy
- Other complications include atelectasis, thromboembolism, infection, and air embolism

Air embolism is a frequently overlooked lethal complication of pulmonary injury. It occurs when air from a torn bronchus enters an adjacent torn pulmonary vein and returns to the left heart. Air in the left ventricle impeded LV filling and during systole gets ejected into the systemic circulation and the coronaries. The typical scenario is a patient with penetrating chest injury who arrests after being placed on positive pressure ventilation.

Indications for Urgent Intervention

1. Cardiovascular Collapse in ER
2. Major Haemorrhage : Immediate drainage of over 1500 ml in chest tube or more than 250 ml / hr
3. Massive Air Leak
4. Pericardial Tamponade
5. Tension Pneumothorax
6. Open Pneumothorax
7. Gross Flail Chest

The first two indications may mandate an emergency department thoracotomy (EDT). This is best accomplished using a left antero-lateral thoracotomy and a longitudinal pericardiotomy anterior to the phrenic nerve. Any cardiac damage is then dealt with . For major bleeding below the diaphragm – the descending thoracic aorta is clamped. Major pulmonary injuries are dealt with by freeing the inferior pulmonary ligament and then placing a hilar clamp (the lung can also be simply twisted on its pedicle for vascular control).



Emergency Thoracotomy in ER (antero-lateral thoracotomy)

Diagnosis

Physical examination

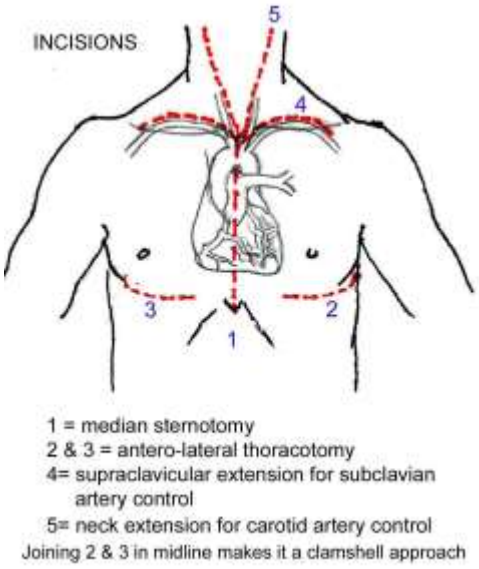
This is vital. Specific attention should be paid to vitals and to the external injuries, chest wall movement, any flail segment, subcutaneous emphysema, bony crepitus, tracheal position, auscultation, and estimated trajectory of the missile wound and examination of the patient's back.

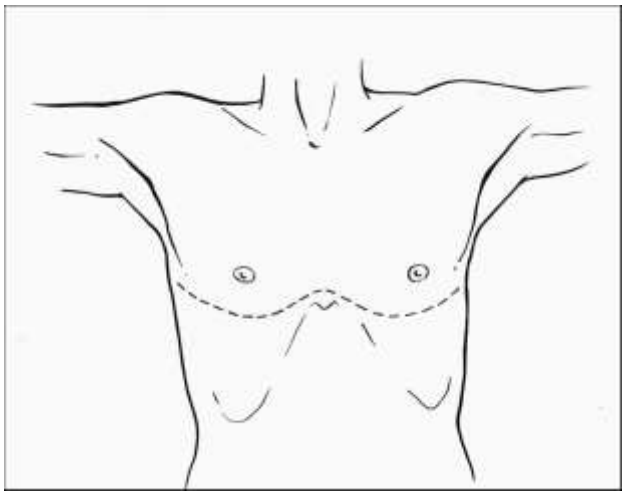
Investigations

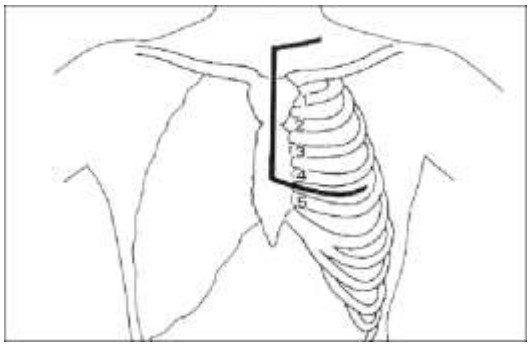
- Basic blood tests : Hb, LFT, RFT
- Chest X Ray
- Ultrasound
- CT Chest
- CT Angiography
- Conventional angiography in very selected cases

Thoracic Incisions

1. *Antero-lateral thoracotomy* is the choice for most emergency approaches. It can be extended if required across the sternum (clam shell incision). This incision can access the heart, lungs , aortic arch , great vessels and esophagus
2. *Median sternotomy* – preferred approach if the injury is on the heart eg stab anterior chest wall with tamponade. It can be extended into the neck to control the vessels of the thoracic outlet




Clamshell incision


Left hemi-clamshell incision

Conclusion

Thoracic injury is directly responsible for 25% of trauma deaths and contributes to death in another 25%. With a rapid action team available 24 X 7 and a strict following of standard protocols a good outcome can be had in this subset of patients who otherwise can have a high mortality.

Liver Trauma

Manoj Andley.

Injuries to the liver are quite common and have been reported to occur in 35% to 45% of patients with severe abdominal trauma. Throughout the past century, the treatment of hepatic injuries has often been a divisive and contentious issue in the management of the trauma patient. Changes from nonoperative management for blunt trauma in the early part of the 20th century to aggressive operative treatment after World War II with a more recent return to the frequent use of nonoperative strategies have led to significant confusion over the appropriate method of treating hepatobiliary trauma. With improved modalities for abdominal imaging and acceptance of nonoperative management for blunt injuries in the modern era, the primary focus for the surgeon has shifted to the selection of appropriate patients for this type of treatment with operative options reserved for failure of observational strategies. The treatment of penetrating hepatic injuries has generally remained

standard with reliance on an operative approach. There have been two significant events that have changed the approach to major hepatic trauma : pioneering work in the anatomy of liver and the new operative techniques for elective hepatic resection.(liver transplant operations have influenced the surgeons' ability to perform hepatic isolation procedures).

Pathophysiology

The amount of damage caused by penetrating missiles to the liver is determined by the kinetic energy. This kinetic energy is a reflection of the mass of the missile, the differential of the velocity of the missile as it enters the tissue, and the velocity of the missile as it exits

Blunt trauma typically results from direct compressive forces or shear forces. The elastic tissues within arterial wall make them less susceptible to tearing than any other structure within the liver. Venous and biliary ductal tissue is moderately resistant to shear forces; the liver parenchyma is the least resistant of all. Thus, fractures within the liver parenchyma tend to occur along segmental fissures or directly into the parenchyma, causing shearing of lateral branches of major hepatic vein and portal veins.

With severe deceleration injury, the origins of the hepatic veins may be ripped from the cava, causing devastating hemorrhage. Similarly, the small branches from the caudate lobe entering directly into the cava are at high risk for shear, and thus a linear tear appears on the anterior caval surface. Direct compressive forces usually cause tearing between segmental fissures in an anteroposterior sagittal orientation. Horizontal fracture lines into the parenchyma give the characteristic burst pattern to such liver injuries. These usually underlie the ribs and costal cartilage. Fracture lines that are parallel have been dubbed 'bear claw' type injuries. Occasionally, there will be a single fracture line across the horizontal plane of the liver, usually between the anterior and posterior segments. Because this fracture line involves both lobes of the liver, it can cause significant hemorrhage if there is direct extension or continuity with the peritoneal cavity.

Knowing the mechanism of injury articulated by the paramedics allows the surgeon to anticipate certain patterns of injury. Compressive forces caused by the steering wheel or the shoulder belt of a three-point restraint system can result in extensive bear claw type injuries to the liver and even transections of the liver . Another example is the so-called T-bone auto crash, which is a crash of two vehicles in a perpendicular fashion. Extensive injury can occur to the liver, usually when the T-bone is into the passenger side, which causes extensive right lateral rib fractures and compression of the right lobe of the liver. An extreme form of this lateral compressive injury is a transverse fracture through both lobes of the liver. Shear injuries are usually associated with deceleration from falls (from a distance greater than two floors) or unrestrained occupants in high-speed motor vehicle accidents. The abrupt deceleration tends to tear the relatively heavy liver from its attachments, such as hepatic veins, veins from the caudate lobe, and lacerations into parenchyma at the ligamentum teres, which are often associated with exsanguinating hemorrhage.

Diagnosis

Initial Evaluation

The assessment and resuscitation of trauma patients undergoing evaluation for hepatobiliary injury are initially no different than for any other injured patient. General principles of the Advanced Trauma Life Support Program as promulgated by the American College of Surgeons should be followed and the response to resuscitation monitored. Special attention is paid to the patient's abdominal examination, vital signs, and response to resuscitation. The specific goals of the initial resuscitation in all patients entail (1) determining, in an efficient manner, the presence of potentially life- threatening injuries; (2) assessing the hemodynamic stability of the patient; and (3) initiating a therapeutic plan that is based on the initial response to resuscitation and findings on the initial surgeon-performed ultrasound, DPL, or abdominal computed tomography (CT) scan. The response to resuscitation serves as an early decision point in the initial treatment of patients with hepatobiliary injuries. Rarely, a patient with major hepatic trauma can present in a hemodynamically stable condition from penetrating wounds.

The evaluation of the patient will be dependent to a considerable degree on the mechanism of injury. Patients with gunshot wounds (GSWs) that enter the peritoneal cavity will require a celiotomy in

virtually all circumstances. There are a few highly selected reports of a small number of patients with hepatic GSW that are followed without operation, but this treatment in no way constitutes the standard of care. In addition to concerns about the liver injury itself, the risk of associated intraperitoneal injury is so high that celiotomy should generally be practiced. Hemodynamically stable patients with stab wounds can often be followed if their physical examination is unremarkable, with operative treatment reserved for those with a change in their clinical status. Patients who sustain blunt trauma and have hemodynamic instability or signs of peritonitis on examination are candidates for urgent operative intervention. However, with the exception of shock, blunt hepatic trauma rarely causes findings on physical examination that mandate the need for surgical exploration. Bruising over the right thoracoabdominal area may suggest blunt force application in the area of the liver, and right lower rib fractures should arouse suspicion for hepatic trauma, but most patients who require an operation for a blunt hepatic injury have relatively few specific abdominal findings. Therefore, additional diagnostic tests are useful for the initial triage and management of those at risk for liver injury. In most trauma centers, the diagnostic modality of choice is an ultrasound evaluation preferably performed by a surgeon (although many emergency physicians may have such training and skills as well). The focused abdominal sonogram for trauma (FAST) is an effective technique for rapid imaging in hemodynamically stable or unstable patients with possible hepatic injuries.

A sagittal view of the right upper quadrant is performed by placing the transducer on the anterior axillary line between the tenth and eleventh ribs. The presence of an anechoic stripe in the hepatorenal fossa or in the right subdiaphragmatic area is strongly suggestive of blood accumulation in the right upper quadrant. While this fluid may represent hemorrhage from other organs in the abdomen, the patient with blunt trauma to the right upper quadrant or flank is likely to have an injury to the liver. The hemodynamically stable patient with a “positive” ultrasound then undergoes a spiral CT of the abdomen to document the presence and magnitude of injuries to the liver and other intraabdominal viscera, whereas the hemodynamically unstable patient with a “positive” ultrasound is moved directly to the operating room without further imaging. A search for extra- abdominal injuries contributing to shock should be undertaken in patients with persistent hemodynamic instability with a negative FAST. If extra-abdominal sources of shock are not present or if hemoperitoneum remains a concern in an unstable patient with a negative FAST, a diagnostic peritoneal aspirate could be performed or the patient may require an exploratory celiotomy.

In emergency departments where major trauma is encountered less frequently, the use of ultrasound occurs infrequently because of lack of equipment and an experienced operator. In these circumstances, CT scanning is generally employed as the primary diagnostic modality in stable patients. A spiral CT of the abdomen and pelvis in the hemodynamically stable patient performed after the intravenous injection of contrast remains the most sensitive and specific imaging modality for the evaluation of hepatobiliary trauma. The value of administering oral contrast before initiation of the scan is debated continuously but is generally not necessary for the evaluation of traumatic injuries. Spiral CT findings of interest to the surgeon include the presence and magnitude of the hepatic parenchymal injury, the presence and magnitude of intraperitoneal blood, and the presence and magnitude of associated intraperitoneal and retroperitoneal visceral, mesenteric, and vascular injuries. Hepatic injuries typically noted on a spiral CT study include a parenchymal laceration, intrahepatic hematoma, or sub- capsular hematoma with or without active extravasation of intravenous contrast.

Experience gained in the past two decades has demonstrated that CT scans are highly accurate in detecting the liver injury itself and aiding the decisions on the need for further intervention—either operation or angiographic embolization. Numerous studies have confirmed the reliability of CT scanning as an accurate tool for the diagnosis and assessment of blunt hepatic injuries. There are three issues that occasionally arise that the surgeon must consider in using this tool: (1) the occasional lack of correlation between the CT scan and the clinical or operative findings; (2) the controversy surrounding intraparenchymal extravasation; and (3) the reliability of scanning in the detection of associated hollow viscus injuries.

Although CT scanning is highly reliable for the diagnosis of hepatic injuries, it may be less accurate in grading injuries. Whether there are patterns of injury on CT scans that are particularly ominous remains controversial, but it is clear that on many occasions the CT scan does *not* provide accurate guidance as to the need for operation. Occasionally, patients with trivial-appearing parenchymal injuries on CT scan are hemodynamically unstable and require a celiotomy. Likewise, most

experienced trauma surgeons have observed patients with major injuries obvious on CT scan who are hemodynamically stable often with little hemoperitoneum. Thus, the need for operation should be determined by clinical factors, most notably hemodynamic stability, rather than CT findings.

A second area of note regarding CT scanning involves the findings of suspected intraparenchymal hemorrhage or pseudoaneurysms within the liver. If an area of suspected hemorrhage as identified by a contrast blush is noted in a hemodynamically unstable patient, then an intervention is clearly needed. This may involve angiographic embolization, although most surgeons loathe transporting an unstable patient to an angiography suite. Patients who can be stabilized may have selective embolization if that capability is available or if no operation likely will be required. On occasion, a patient has CT evidence of extravasation but is very stable and has little evidence of blood loss. Whether that patient requires angiography and embolization is problematic although most algorithms follow such a course.

The third area of concern regarding CT scanning of suspected liver injuries involves its reliability in detecting visceral injuries. Associated intestinal injuries occur in about 2% to 6% of most series of liver injuries, and their diagnosis may be problematic. The blood from a hepatic injury may obscure the fluid from a perforated intestinal segment and clinical findings of intestinal injury may be masked by sedation, need for mechanical ventilation, or associated injuries causing distracting pain. It is imperative that intestinal injuries be considered in appropriate clinical circumstances, regardless of negative CT findings.

DPL was once the mainstay of the diagnosis of intra- peritoneal bleeding but its use has been greatly curtailed in the past two decades. Although some units continue to use it selectively, others do so rarely, and currently it is rarely considered indicated in the evaluation of hepatic injuries. Laparoscopy has been useful in selected circumstances for the diagnosis and possible treatment of some intraabdominal injuries but its role in the primary management of liver injury is minimal if any. Some surgeons frequently uses laparoscopy as an adjunct to manage bile ascites postinjury.

Classification of Liver Injuries

The American Association for the Surgery of Trauma (AAST) developed the Hepatic Organ Injury Scale in 1989 and revised this system in 1994. At the time of its development, the scoring system was based on operative findings . Grade I injuries were generally minor and they increased in severity to a grade VI injury, which denoted complete avulsion of the liver. In an ideal system, as severity increases, the need for more aggressive interventions increases, as does mortality. Although the classification system for liver injuries has many useful features, it has some inherent problems. First, the system was developed for operative findings and there is less evidence of its applicability to CT scan evaluation of injuries. Second, although there is a general worsening of outcomes with more severe injuries, that is, grade IV and V injuries are more likely to require operation, the majority of even these more severe injuries still do not require operative treatment. On occasion, less severe grades may injure a peripheral vascular structure with consequent major bleeding requiring operation. Thus, the system has general utility for the management of liver injuries and a greater value in reporting the results of treatment, but it is not specific enough to be useful in a protocol for the treatment of these problems. Several authors have noted this lack of correlation and have suggested other systems, but to date a better grading mechanism has not been adopted.

Anatomic classifications of the liver have been developed by Couinaud and Bismuth based on segmental anatomy of vessels and bile ducts. These classifications are widely used in planning elective operative treatments and describing outcomes for a number of hepatic operative procedures. Occasionally, a surgical oncologist with an interest in the liver will editorialize on the failure of those interested in hepatic trauma to use these anatomic classifications in either the treatment or reporting of liver injury. Generally, injuries to the liver do not correspond to anatomic segments and most trauma surgeons have not found these classifications useful in their treatment of hepatic injuries.

Principles Of Operative Management

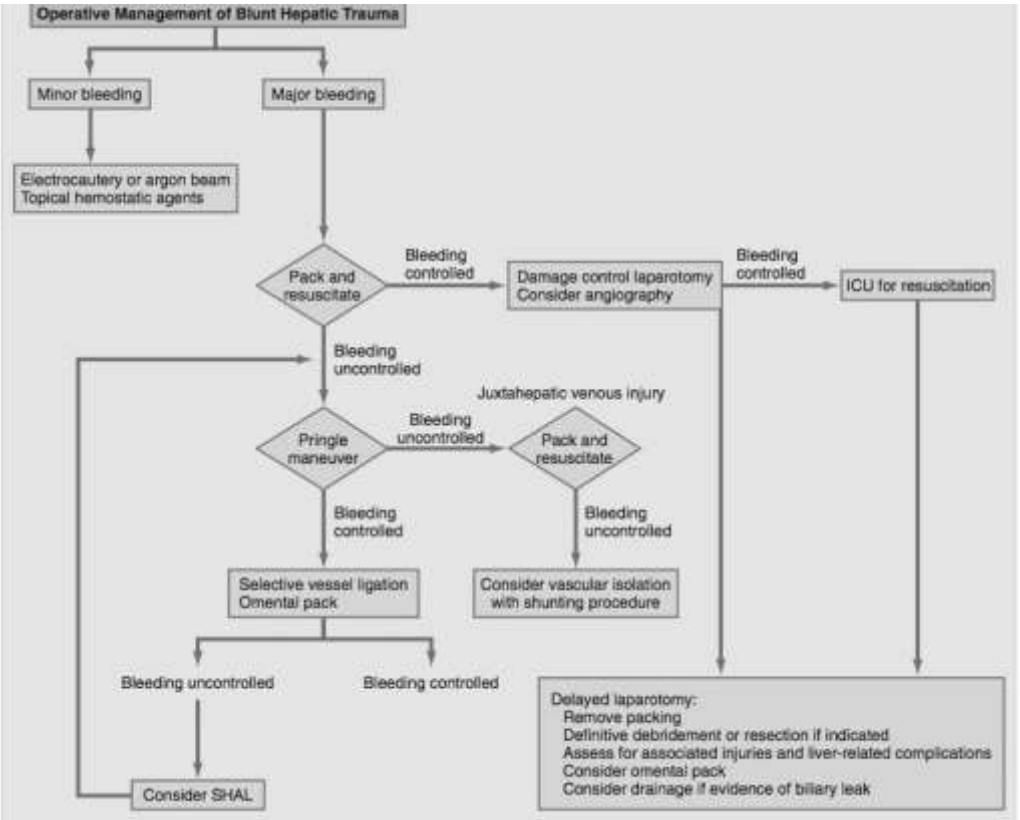
Operations for trauma should utilize a midline incision (whether done for blunt or penetrating injury) to permit rapid exploration of the entire abdomen.

AAST (American Association of Surgery of Trauma) Liver Injury Scale

Grade		Description
I.	Hematoma	Subcapsular, nonexpanding <10 cm surface area
	Laceration	Capsule tear, nonbleeding <1 cm depth
II.	Hematoma	Subcapsular, nonexpanding 10% to 50% surface area Intraparenchymal nonexpanding <10 cm diameter
III.	Hematoma	Subcapsular, >50% surface area or expanding, ruptured
	Laceration	<3 cm depth (parenchyma)
IV.	Hematoma	Ruptured intraparenchymal hematoma with active bleeding
	Laceration	Parenchymal disruption 25% to 75% of lobe
V.	Laceration	<75% parenchymal disruption
	Vascular	Juxtahepatic venous injury
VI.	Vascular	Hepatic avulsion

The conduct of the operation will be determined to a considerable degree by the extent of hemoperitoneum encountered and the site of the presumed source of bleeding. If a large volume of free blood is encountered, packs should be placed in the four quadrants of the abdomen in an attempt to determine the primary site of bleeding. If liver bleeding can be controlled with packs, these can be left in place while other potential injuries are evaluated and/or addressed.

Minor bleeding from hepatic trauma may occur in association with other intraabdominal injuries and is often due to low-grade (I and II) liver injuries. These minor injuries can usually be managed by compression and temporary packing alone or with electrocautery, argon beam coagulation, or topical hemostatic agents as adjuncts to speed hemorrhage control. Packing with tem- porary abdominal closure will rarely be required for these low-grade injuries. However, for more severe hepatic injuries (grade III to V) a stepwise approach to the patient with massive bleeding is required for successful outcome.



The Western Trauma Association proposed this algorithm for management of blunt liver injuries requiring operation. SHAL, Selective hepatic artery ligation.

The primary method of hemorrhage control is manual compression followed by perihepatic packing. The surgeon compresses the injured parenchyma between two hands and places laparotomy pads around the liver to both compress the injury and to assist in hemostasis

If massive bleeding not amenable to temporary control is encountered, it must be addressed immediately. Bimanual compression usually permits arrest of most parenchymal bleeding and will permit resuscitative efforts by the anesthesiologist. The operative strategy will then be determined by the extent of the hepatic injury and the amount of bleeding encountered. If significant bleeding occurs, activation of a massive transfusion protocol should be strongly considered. Additionally, prevention and correction of hypothermia and acidosis should be instituted to minimize blood loss from coagulopathy.

There is no single method or technique that will ensure successful control of hepatic bleeding. Therefore, the surgeon may need to consider a variety of options depending on the geometry and depth of the wound and the nature of vessels injured

Bleeding parenchymal injuries are best managed by vessel ligation if feasible. Bleeding from within the depths of the parenchyma may require removal of liver tissue to expose the bleeding vessels. The use of the finger fracture technique will remove devitalized liver tissue and permit exposure to perform suture ligation of bleeding vessels.

When major bleeding occurs, control of the porta hepatis should be promptly employed. In cases of massive bleeding, this may be initially performed by compressing the triad between the thumb and forefinger. A gentle, noncrushing fine vascular clamp can then be applied for more secure control.
It appears the Pringle maneuver can be safely employed for an hour at least.

If the bleeding cannot be controlled surgically or by packing within that interval, it is doubtful further clamping of the triad with surgical maneuvers will salvage the patient. If there is arterial bleeding from deep within the parenchyma not amenable to suture control, there are several options. If the arterial bleeding is arrested with portal triad compression, selective hepatic artery ligation (SHAL) can be performed. It remains an important consideration for the occasional patient with arterial bleeding that is controlled with unilateral vascular occlusion. Some manage uncontrolled arterial hemorrhage by packing the patient and taking him or her to the angiography suite for selective embolization.

If the Pringle maneuver fails to even temporarily control arterial bleeding, one should consider an aberrant left hepatic artery in the lesser omentum as the bleeding source. There are reports on the use of tractomy for exposure of deep arterial bleeding. In this procedure, a tract is opened to expose the area of bleeding. This procedure may not be as commonly used at present because many of these patients are now treated by embolization.

Hepatorrhaphy or reapproximation of the liver parenchyma may be useful for control of venous bleeding or bile leakage. The technique usually involves the placement of large absorbable sutures, often in mattress fashion, for the reapproximation of the liver. Small bleeding cracks can often be closed with the arrest of hemorrhage by this technique without causing tissue necrosis or unnecessarily extending the wound by tractomy or finger fracture.

After the major vessels and ducts have been controlled by suture techniques, the gentle reapproximation of the divided portions occasionally decreases oozing from the raw surfaces. This technique may be augmented by an omental flap, packing, or both. If used appropriately, hepatorrhaphy can be a useful tool, but it will not control major arterial bleeding. Omental pedicle flaps can be very useful for prevention of diffuse oozing from raw surfaces of the liver. Formal anatomic resection of the liver is not commonly indicated for trauma as it would be for oncologic issues.

Operative Techniques in Liver Trauma
Individual vessel ligation
Large mattress sutures
Hepatic artery ligation
Resectional debridement
Hepatic lobectomy (or major resection)
Omental packing
Packing and planned re operation

There are several instances where a major hepatic resection is indicated: devitalizing injuries along anatomic planes, completion lobectomy when the injury has transected the liver along lobar anatomy, and for exposure of major venous bleeding associated with a major hepatic parenchymal injury.

Major Venous Bleeding

Although major arterial hemorrhage must be controlled by surgical or radiologic means and is not amenable to cessation by packing, major venous bleeding is a great impediment to patient survival as well. Major venous bleeding may result from injury to one of the main hepatic veins, from a major injury associated with the vena cava, or from a retrohepatic vena cava wound itself. Isolated vena cava lacerations without involvement of a hepatic vein branch are unusual in blunt trauma but may occur with a GSW. Major hepatic venous injuries confined to the liver parenchyma can generally be success- fully managed by suture ligation. If the injury is not readily apparent and blood is welling up from a deep crevasse, it may be necessary to expose the venous injury more clearly with finger fracture or tractomy. Suture ligation can generally be used to control hemorrhage. Once major bleeding has been lessened, packing may be used to control the remaining bleeding.

Avulsion of the hepatic veins from the vena cava is potentially a lethal injury. On occasion, this problem can be solved by packing the area of injury and allowing the low-pressure venous system to tamponade. However, the packing may not succeed in hemorrhage control and if the packs are placed too aggressively, the venous return from the lower body may be totally interrupted, with resultant unsustainably low cardiac output. Using inflow occlusion, the bleeding may be decreased enough to allow suture control but inflow occlusion of the portal triad does not prevent back- bleeding from the vena cava. One can use direct application of fine vascular clamps to reapproximate the anterior wall of the vena cava and the major hepatic veins with good success. The clamps can be allowed to remain in place with the abdomen packed in a damage control strategy. There have also been a few reports of successful management by the use of fenestrated endovascular stent grafts. This method usually involves a contained injury, in which extravasation was demonstrated on a CT scan.

Historically, the method of choice for management of juxtahepatic major venous injuries has involved the use of an atriocaval shunt. The concept involves the placement of a tube of some type (usually a thoracostomy or endotracheal tube) through the right atrium into the inferior vena cava. Snares are used around the cavae above and below the liver in an attempt to divert flow through the tube and away from the area of injury, permitting a bloodless field and, theoretically, a more controlled repair. This operation requires an incredible amount of skill and good fortune to be successful.

It requires opening a second body cavity (the thorax), which worsens hypothermia and bleeding, and many wounds are difficult to repair even if the shunt is functioning. Suffice it to say, juxtahepatic venous injuries remain an unsolved problem in hepatic trauma, no single technique is successful, and no algorithm for management can be constructed with a reason- able likelihood of patient survival.

Perihepatic Packing & Damage Control Strategies

Perihepatic packing has been demonstrated to have a major survival advantage in patients who would have likely died with conventional surgical treatment. The term *damage control*, in which packing is an integral part of that strategy, has become a recognized and accepted concept.

Tenets of Hepatic Packing

- Choose appropriate patient
    - Control arterial bleeding surgically/arteriographically
    - Ideal for lesser venous bleeding, coagulopathy
- Use before excess bleeding and coagulopathy develops (patients often have acidosis and abnormal coagulation profile in emergency department- unlikely to control bleeding surgically)
- Pack to compress liver in superior to inferior place; anteroposterior packing tends to compress the vena cava
- Count Sponges (if feasible; facilitates later removal)
- Some use nonadherent material over liver
- Temporary abdominal closure must avoid tension and secondary abdominal compartment syndrome

The tenets of liver packing begin with the choice of an appropriate patient; arterial hemorrhage will likely require control by suture or embolization. Good judgment is required to not forego appropriate attempts at technical control of bleeding without delaying for an inappropriate time, which might prevent patient survival. Secondary effects of abdominal compartment syndrome can generally be ameliorated by avoiding fascial closure, often accompanied by some method of temporary closure usually involving a dressing or vacuum pack technique. Some advocate return to the operating suite for pack removal when the patient is rewarmed and coagulopathy corrected. These goals may be accomplished within 6 hours. However, preferred method is to leave packs for 24 hours to allow for coagulation of exposed vessels that may rebleed with early pack removal.

Nonoperative Management (NOM)

As imaging with CT scans has became prevalent, it has allowed a diagnosis to be made without DPL and also permitted evaluation of other intra abdominal injuries.

About 80% to 90% of hepatic injuries can be safely managed without operation. Although the guidelines for NOM may vary slightly, the principles are fairly well standardized. The key factor in determining whether NOM can be safely used is hemodynamic stability. Most trauma centers will permit up to four units of blood transfusion to be given before celiotomy is required. There should be no evidence of visceral injuries on CT scan. Although a baseline CT scan is almost always performed, operation is usually mandated by the clinical findings of hemodynamic instability and/or ongoing transfusion requirements, and not by the injury grade on CT scan. While patients with a higher-grade injury (as judged by CT) have an increased rate of operation, many patients with high-grade injuries on CT scan do not need operation. Conversely, an occasional patient with a relatively innocuous injury may have bleeding requiring an emergent celiotomy.

Patients who are selected for NOM should be in an intensive care unit environment with careful monitoring of vital signs and hemoglobin level for the first several days postinjury.

Most patients who fail NOM tend to do so quickly and delayed bleeding is rather uncommon.The failure rate after 36 hours for NOM is in the 2% to 3% range. A few patients have ongoing bleeding and some require operations for associated injuries including those to the spleen and delayed recognition of a visceral injury.

There is anecdotal evidence that suggests venous injuries, which are low pressure in nature, may actually heal if operation is avoided.

Adjunctive Treatment Methods

- Angiography / Embolization
- ERCP
- Drains
- Laparoscopy

The use of NOM (non operative management) does not imply that other types of invasive treatments may not be required to treat the patients. Therefore, the mindset for NOM should not be to avoid needed therapeutic interventions but to allow the patient to recover as rapidly as possible, which may require adjunctive procedures. Angiography may be very useful for patients with an arterial blush on CT or evidence of arterial extravasation on angiography. Delayed bleeding from hemobilia may require angiographic treatment as well. Patients with prolonged bile leaks may be improved by endoscopic retro- grade cholangiography with possible sphincterotomy and biliary stent placement.

Patients with perihepatic fluid collections may benefit from percutaneous drainage. However, the radiologic placement of small-caliber drains around the liver will not remove the liters of blood and bile distributed in all four abdominal quadrants and the pelvis. When large accumulations of blood and bile are present, they may cause bile peritonitis, a systemic inflammatory response syndrome (SIRS), or an abdominal compartment syndrome. To prevent and/or treat these problems, laparoscopy can be performed for evacuation of a major accumulation of blood and bile when the patient is stable after 3 or 4 days. Laparoscopy permits the evacuation of virtually all of the fluid from the abdominal quadrants and the pelvis itself. Do not attempt to remove organized clot from around the liver and generally place a perihepatic drain to monitor subsequent bile output.

Subcapsular Haematoma

Subcapsular hematomas occur in about 2% to 3% of major blunt liver injuries. The natural history of subcapsular hematomas is not clearly defined, but unlike a similar injury to the spleen, which has a real risk of delayed rupture, subsequent bleeding seems to be much less in common hepatic hematomas. If subcapsular hematomas are encountered, indications for further operative intervention include continued expansion of the hematoma and management of its rupture. Arteriography and embolization may be useful for expanding lesions. If a suspected subcapsular hematoma is detected on CT scan, no therapy is recommended unless it is associated with an arterial blush, suggesting the possibility of continued bleeding. In such instances, angiographic embolization is recommended. If the capsule is ruptured, then operation may be required to control the diffuse bleeding from the exposed surface of the liver. Temporary packing will usually control such bleeding and an omental flap may be useful to prevent rebleeding.

Hemobilia

Hemobilia is defined as bleeding from the liver which is expressed from the biliary tree. Typically, the bleeding begins several days to a few weeks postinjury and may be manifested by several clinical presentations. Occasionally, patients may present with brisk upper gastrointestinal bleeding, although melena is somewhat more common. Jaundice or sub- clinical evaluation of bilirubin is frequently present. Hemobilia should be suspected in those who sustained recent liver injury with gastrointestinal bleeding and/or jaundice.

The diagnostic modality of choice is arteriography, which commonly shows an abnormality within the liver parenchyma. Selective embolization of the vascular abnormality is nearly always effective in treating this problem, and operation is rarely required. Operative treatment is indicated for failure of angiographic treatment, for debridement of associated necrotic liver, or for intrahepatic sepsis.

Bilehemia

In contrast to hemobilia where bleeding occurs through the biliary system, bilehemia is an abnormal communication between an intrahepatic bile duct and a vein. The bile flows into the venous system and may result in profound jaundice. There are few reports of bilehemia in the literature, but most require a two-pronged approach aimed at obliterating the offending vessel through angiographic techniques and decompression of the biliary system through endoscopic retrograde cholangiography and stenting.

Avulsion of Liver

Grade VI injuries consist of total avulsion of the liver. Although most of these injuries are rapidly fatal, an occasional patient survives his or her operative treatment. There are several reports of successful venovenous bypass with the patient in an anhepatic state followed by emergency liver transplantation. These cases require a mindset of preparedness and ingenuity to salvage an otherwise fatal situation.

Gallbladder Injuries

Injuries to the gallbladder may result from either blunt or penetrating trauma. Regardless of mechanism, isolated gallbladder injuries are relatively uncommon. The treatment of choice should be cholecystectomy, and the outcome will be determined by the presence and extent of associated injuries. Attempts to repair even minor gall- bladder injuries should generally be avoided because of the propensity for bile leakage and the risk of gallstone formation engendered by the inflammation around the suture used for repair. Acalculous cholecystitis may also follow treatment modalities that interrupt the gallbladder's blood supply. Both selective hepatic artery ligation and angiographic embolization of the hepatic artery commonly lead to acalculous cholecystitis and may result in gallbladder necrosis. If a selective right hepatic artery ligation is performed, we recommend concomitant cholecystectomy to prevent this problem.

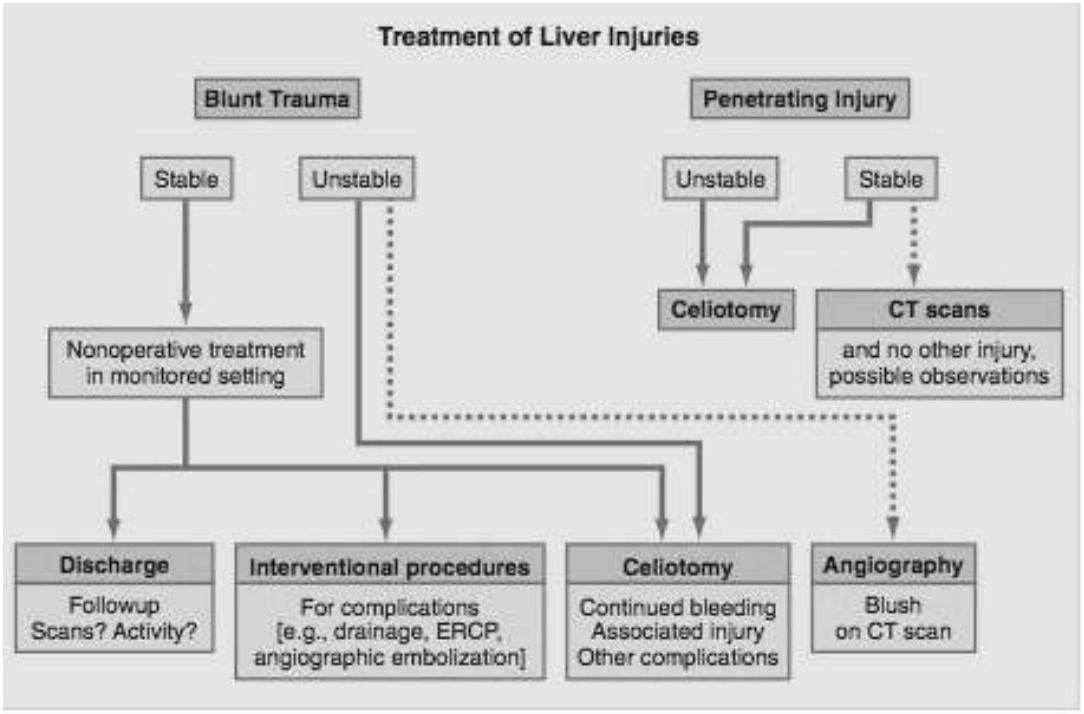
Injuries of The Extrahepatic Bile Ducts

Injuries of the extrahepatic bile ducts may follow both blunt and penetrating injuries and, as in the

case of gall- bladder injuries, rarely occur in isolation. Several text- books suggest these injuries may be managed by techniques commonly employed to manage iatrogenic complications such as bile duct injury occurring during a cholecystectomy. In our experience of more than 35years of managing such injuries (which are fortunately not common), the parallels between iatrogenic injuries and either blunt or penetrating trauma have little in common. When the extrahepatic ductal system is injured by penetrating injuries, other structures are invariably injured, and given the close approximation of the bile ducts to major vessels, massive hemorrhage often accompanies such injuries. Embarking on a choledochojejunostomy to definitively repair a ductal injury may not be prudent with a patient recently in hemorrhagic shock or having coagulopathies.

When the extrahepatic ductal injury is due to blunt trauma, a tremendous force is required to produce extra- hepatic ductal injury. This usually results in associated injuries to the liver, pancreas, duodenum, or other structure and/or a devastating ductal injury. Clean transections of the ductal system are rarely, if ever, encountered and the duct is often totally devascularized or completely avulsed from the liver bed or duodenum.

Given both the complexities of these injuries, the diversity of anatomic disruptions, the myriad of associated injuries, and, fortunately, their rarity, it is not practi- cal to propose an algorithm for the management of extrahepatic ductal injuries. The axiom “if you have seen one ductal injury, you have seen one ductal injury” might well apply. If the patient were stable, had no other major injuries to address and had a structural configuration amenable to early repair with choledochojejunostomy, or hepaticojejunostomy, such would be a logical approach. Since these conditions rarely are encountered, other strategies are often necessary. If it is feasible to place a T-tube or some type of tube in the remaining biliary structures for drainage, that is a step we recommend. Unfortunately, given the aforementioned difficulties each case may present, the surgeon must often be creative in attempting to manage these most challenging problems. After the patient has been stabilized, the ductal system can be evaluated by ERCP, via a T-tube if that was placed intraoperatively or by a transhepatic route. Delayed reconstruction can then be planned as needed.



Broad Outline for Management of Liver Injuries

Hormonal manipulation in Carcinoma Breast- as Adjuvant therapy

Geeta Kadayaprath

Adjuvant endocrine therapy with tamoxifen for premenopausal women and aromatase inhibitors for post menopausal women is the standard of care in women with hormone receptor positive breast cancer, which accounts for almost 75% of all breast cancers. Hormonal treatment is also the first line of treatment in women with hormone receptor positive, Her-2-neu negative, metastatic breast cancer.

Oophorectomy - or ovarian ablation (OvA) - was the first form of systemic treatment for breast cancer[1]. The first surgical oophorectomy in a patient with metastatic breast cancer is credited to Beatson, performed in 1896.

Combined analysis of several small trials testing ovarian ablation through the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has unequivocally established that OvA as a single intervention reduces recurrence and increases survival for women younger than 50 years of age for both axillary node-positive and node-negative disease.[2]

Tamoxifen

The introduction of Tamoxifen in the treatment of breast cancer was a revolution of sorts. The first randomized trials showed the benefit of tamoxifen as adjuvant treatment, in a big way.
Results of the first randomized trials –

Nolvadex Adjuvant Trial Organization- 1285 women were randomized to Tamoxifen 10mg BD for 2 years or no further treatment.
Result-At a median follow up of 5.6 years, tamoxifen treated patients had a 36% reduction in the risk of event (p=.0001) and a 29% reduction in the risk of death from all causes.(p=.006).

NSABP B-14 trial - 2644 women with ER +, node negative breast cancer were randomized to tamoxifen 10mg BD vs placebo for 5 years.
Result- On follow up at 15 years, patients who had been treated with Tamoxifen, showed significantly better recurrence free survival (78% vs 65%, p<.0001) and overall survival (71vs 65%,p=.0008) compared to placebo.

The first Oxford EBCTCG meta-analysis- involved almost 30,000 women in 28 trials with either node- positive or node-negative breast cancer who were randomly assigned to tamoxifen (or not) for about 5 years [3].
Result- It demonstrated a clear reduction in mortality in women at least 50 years of age treated with tamoxifen (P <0.0001) and a reduction in the annual odds of death during the first 5 years of about 20%.

5 years is better than two years

Early Breast Cancer Trialists Collaborative Group meta-analysis,
Median follow-up of 13 years -5 years of Tamoxifen compared to no endocrine treatment in ER+ disease,was associated with a reduction in breast cancer recurrence by 39% [4].

At 15 years-Absolute reduction in risk to recurrence was 13% (33% vs 46%). The relapse curves did not converge after year 10 (RR = 0.97 in years 10 to 14); therefore, a high proportion of patients receiving tamoxifen for 5 years can be potentially cured.

The magnitude of benefit was greater for women with node positive disease. It is amply clear from the meta analyses that full compliance with 5 years of Tamoxifen reduces 15 year mortality by at least 30% and more[4,5].

Tamoxifen for 10 years is still better
Late failures on treatment with tamoxifen for 5 years raised the question of prolonging hormonal treatment.

Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial tried to answer this question.

The Study group-6,846 women with ER+ disease were randomly assigned to

1) continue tamoxifen treatment to 10 years
2) to discontinue after 5 years

Results-

1) 10 years of tamoxifen further reduced the risk of relapse (P = 0.002), breast cancer mortality (P=0.01), and all-cause mortality (P= 0.01) compared with 5 years 6[113].
2) A persistent and more significant effect was found after year 10 (RR 0.90, 95% CI, 0.79-1.02 during years 5-9 and 0.70, 95% CI, 0.62-0.90 during subsequent years).
3) Survival benefit became apparent only after completion of 10 years of tamoxifen. There was a 29% reduction in the risk of breast cancer mortality after year 10 (RR 0.71,95%CI).
4) The most important AEs on prolonged treatment were an increased risk of endometrial cancer (RR = 1.74) and PE (1.87) after 10 years of treatment, with a lower risk in premenopausal women. However there was no increase in the incidence of stroke incidence, and a decrease in incidence of ischemic heart disease was noted (0.76).

Overall the benefits of extended tamoxifen seemed to substantially outweigh the risks.

Adjuvant Tamoxifen-To Offer More? (aTTom) trial randomly assigned 6,953 UK women in remission after 5 years of tamoxifen to 5 more years of tamoxifen or to stop [7] . The breast cancer recurrence rates were 16.7% in the 10-year study group and 19.3% in the 5-year study group. Longer treatment also reduced breast cancer mortality in a time- dependent fashion with RRs of 1.03 during years 5 to 9 and 0.77 later and overall mortality RRs of 1.05 during years 5 to 9 and 0.86 later.).

The pooled analysis of the UK aTTom and the international ATLAS trials showed better results in terms of recurrence, breast cancer mortality, and OS benefits [7]However, it is important to follow up these patients carefully and perform a metaanalyses of all relevant trials to ascertain the risk benefit ratio of extended hormonal treatment.

Ovarian function suppression/ablation (OFS /OA)

Surgery, radiation or LHRH agonists can achieve ovarian suppression or ablation.

THE EBCTG overview

OA or OFS with LHRH agonists significantly reduce the risk of recurrence and breast cancer mortality in women <50 years[8]. The effect was smaller in women who received chemotherapy.

ECOG-led Intergroup 0101 trial

In premenopausal women with ER+ node-positive early breast cancer, the addition of both tamoxifen and goserelin improved DFS as compared to chemotherapy alone but no significant effect on DFS was shown with the addition of goserelin alone. A trend to DFS benefit from addition of goserelin to chemotherapy was demonstrated in an unplanned retrospective analysis of women <40 years [9].

International Breast Cancer Study Group (IBCSG) trial VIII

Premenopausal women with node-negative ER+ early breast cancer were randomized to either adjuvant CMF, goserelin for 2 years, or CMF followed by goserelin for 18 months. The addition of goserelin resulted in a small improvement in 5-year DFS but was not statistically significant. However, in an unplanned subset analysis involving women <40 years, significant benefit (HR 0.34; 95% CI, 0.14-0.87) was seen [10].

EBCTG meta-analysis -trials with known ER status and LH-RH agonists for OFS [11].

The Positives

OFS proved to be beneficial whether used alone (recurrence risk reduction of 28%, P=0.08), in addition to tamoxifen or chemotherapy (recurrence risk reduction of 13%, P=0.02), and as an alternative to chemotherapy. The effects of LH-RH agonists were greater in women <40 years in whom chemotherapy is less likely to induce permanent amenorrhea.

The Negatives

There were few trials testing the addition of LH-RH agonists to tamoxifen (with or without chemotherapy)

No trials had compared a LH-RH agonist against chemotherapy with tamoxifen in both arms.

Suppression of ovarian function and Tamoxifen trial (SOFT) and Tamoxifen and Exemestane trial (TEXT)

Whether combined hormonal manipulation compared to Tamoxifen alone improve PFS and OS is being addressed in two large prospective trials.

The SOFT trial will assess the role of OFS/OA in combination with the AI exemestane, compared with OFS plus tamoxifen or tamoxifen alone. Three-thousand-sixty-six women were randomized into this study, which completed accrual in January 2011 [12].

The TEXT trial assesses a LH-RH agonist with the addition of either tamoxifen or exemestane for 5 years (chemotherapy is optional): accrual of 2,672 women was completed in March 2011 [13]. In the initial 890 patients entered in the TEXT trial, chemotherapy was chosen for 64% of patients, lymph node status being the predominant determinant of chemotherapy use (88% of node- positive versus 46% of node-negative) [14].

The results of both these IBCSG-led trials, awaited in the course of 2014, will help the selection of the optimal ET for premenopausal women with ER+ early breast cancer.

Aromatase Inhibitors

Aminoglutethimide (AG) was the first AI to be developed for clinical use [15-17] and showed benefit initially in advanced disease and then as adjuvant therapy [18] However, it fell out of favor due to its side effects.

Today three third-generation AIs are approved for use: anastrozole and letrozole are non-steroidal AIs that reversibly and non-covalently bind aromatase enzyme[19], and exemestane is a steroidal AI that irreversibly and covalently binds aromatase. The potential efficacy and benefit of AIs as adjuvant treatment over tamoxifen have been studied as adjuvant therapy in a number of randomized clinical trials in post-menopausal women, both as upfront treatment and after tamoxifen.

The ATAC trial compared adjuvant tamoxifen with an AI in postmenopausal women with early breast cancer.
Tamoxifen was compared with anastrozole alone or with anastrozole plus tamoxifen for 5 years in 9,366 post-menopausal women, of whom 7,839 (84%) were known to be HR+ [20]. At a median follow-up of 33.3 months, DFS rates of 89.4% for anastrozole and 87.4% for the tamoxifen alone were seen. The combination showed no significant difference to tamoxifen alone. The DFS improvement with anastrozole was seen in HR+ but not in HR− patients. The incidence of contralateral breast cancer was significantly lower with anastrozole than with tamoxifen (odds ratio 0.42, P = 0.007).

After a median follow-up of 120 months, the superior efficacy and safety of anastrozole over tamoxifen as initial adjuvant therapy were confirmed [21].There were significant improvements in the anastrozole group compared with the tamoxifen group for DFS, time to recurrence (TTR), and time to distant recurrence (TTDR), especially in HR+ patients (2.7% at 5 years and 4.3% at 10 years) and recurrence rates remained significantly lower on anastrozole than tamoxifen after treatment completion, although the carry- over benefit was smaller after 8 years. There was, however, no significant difference in OS (hazard ratio = 0.95, P = 0.4) or in deaths after recurrence between anastrozole and tamoxifen.

Breast international group 1-98 Study
Compared 5 years of adjuvant therapy with tamoxifen or with letrozole or switch after 2 years of one of these agents followed by 3 years of the other in 8010 patients [22]. After a median follow-up of 25.8 months, 5-year DFS estimates were 84.0% and 81.4%, respectively. Compared with tamoxifen, letrozole significantly reduced the risk of a DFS event (hazard ratio = 0.81, P = 0.003) and the risk of distant recurrence (hazard ratio = 0.73, P = 0.001). At a median follow-up of 8.7 years , letrozole alone was confirmed to be significantly better than tamoxifen, not just for DFS but (in contrast to ATAC) also for OS [23].

Intergroup Exemestane Study (IES), Arimidex-Nolvadex 95, ABCSG-8, and the Italian Tamoxifen Anastrozole trials
These trials addressed the issue of switching to an AI after 2 to 3 years of tamoxifen in post-menopausal women with ER+ disease [24-27]. These trials have consistently shown benefit for the switch.

In BIG 1-98, at a median follow-up of 8.0 years from random assignment, there was no significant difference between one of the crossover arms (tamoxifen followed by letrozole) versus letrozole alone, but there was a trend against starting with tamoxifen and then switching.

The multicenter TEAM trial, originally designed to examine the efficacy of exemestane versus tamoxifen in 9,779 HR+ women, was revised in 2004, and patients on tamoxifen were switched to exemestane after 2.5 to 3 years, when the IES showed better results for a switch from tamoxifen to exemestane after 2 to 3 years [28]. At a median follow-up of 5.1 years (60% of patients completed at least 5 years of follow-up), there was no significant difference in outcome between the two groups: DFS rates were 85% in the sequential arm and 86% in the exemestane-alone arm [29], and OS showed no significant difference, being 91% in both arms. In summary, there is no therapeutic gain in starting with tamoxifen and switching to an AI rather than starting with an AI upfront.

Extended adjuvant endocrine therapy

Women with HR+ early breast cancer continue to relapse even up to 15 years after primary diagnosis, despite being on adjuvant endocrine therapy for around 5 years [30,31].

NCIC CTG MA.17/BIG 1-97

These trials tested the effectiveness of 5 years of letrozole after completion of the standard 4 to 6 years of adjuvant tamoxifen and were the first phase III trials to demonstrate an OS advantage with an adjuvant AI [32]. At a median follow-up of 2.4 years, a highly significant reduction in the risk of recurrence was seen with letrozole versus placebo (DFS hazard = 0.57, P = 0.00008) [50], prompting early unblinding to allow patients in the control group to switch to letrozole. At a median follow-up of 30 months, a relative reduction in recurrence risk of 42% occurred with letrozole [33].

Letrozole treatment significantly reduced the risk of distant metastases in both node- negative and -positive patients (P = 0.002) and significantly improved OS by 39% in node-positive patients compared with placebo. At the time of trial unblinding, 1,579 women initially on placebo elected to receive letrozole and 804 women chose no further treatment. At a median follow-up of 5.3 years, a significant reduction in recurrence risk and a significant 61% improvement in DDFS were found in patients who switched to letrozole, although they had more adverse prognostic factors.

The optimal duration of extended adjuvant endocrine therapy remains unclear. Ingle and colleagues [34]suggested that the hazard ratio continues to fall for DFS and DDFS but not for OS at 48 months, indicating that the benefit of letrozole increases with longer exposure. The 66% crossover rate in MA.17 from placebo to letrozole after unblinding offered a good opportunity to test whether delayed initiation of an AI could still be of any benefit [35]. These results suggest that therapy given for more than 7 years after diagnosis can change the chronic relapsing behavior of HR+ breast cancer. They also show that delayed letrozole commencement after stopping tamoxifen can still be of benefit.

ABCSG Trial 6a

HR+ post-menopausal patients who were disease-free after 5 years of adjuvant tamoxifen (with or without Aminoglutethimide) were randomly assigned to 3 years of anastrozole or no further treatment [36]. Anastrazole was found to reduce the risk of a breast cancer event (locoregional recurrence, distant recurrence, or contralateral breast cancer) in the 856 patients enrolled with a median follow-up of 62.3 months, by 38% compared to those who had no further treatment. There was no statistically significant difference in OS between the two arms.

NSABP-B33

This trial investigated extended adjuvant therapy with exemestane in post-menopausal women with clinical T1-3N1M0 BC who were disease-free after 5 years of adjuvant tamoxifen [37]. This trial closed prematurely after the publication of the results of MA.17. At 30 months of median follow-up, ITT analysis showed a trend of improvement in 4-year DFS,91% versus 89% and a statistically significant improvement in 4-year recurrence-free survival (96% versus 94%).

The Adjuvant post-Tamoxifen Exemestane versus Nothing Applied trial compared exemestane versus observation after 5 years of previous tamoxifen [38]. This trial was prematurely closed after recruiting only 448 patients.

The data sets from these trials have been analyzed in an EBCTG meta-analysis [39]. At a median follow-up of 2.5 years, extended adjuvant AI treatment was associated with an absolute 2.9% decrease in breast cancer recurrence (relative decrease of 43%, P <0.00001) and an absolute 0.5% decrease in breast cancer mortality.

ASCO Recommendations- May 2014

Duration of Treatment for Pre and Peri-Menopausal Women

Women diagnosed with hormone receptor positive breast cancer who are pre- or perimenopausal should be offered adjuvant endocrine therapy with:

- *Recommendation IA.* Tamoxifen for an initial duration of 5 years.
- *Recommendation IB.* After 5 years, women should receive additional therapy based on menopausal status.
- *Recommendation IB1.* If women are pre- or perimeno-pausal, or if menopausal status is unknown or cannot be determined, they should be offered continued tamoxifen for a total duration of 10 years.
- *Recommendation IB2.* If women have become definitively postmenopausal, they should be offered the choice of continuing tamoxifen for a total duration of 10 years or switching to up to 5 years of an AI, for a total duration of up to 10 years of adjuvant endocrine therapy.

Adjuvant Endocrine Treatment and Duration in Postmenopausal Women

- *Recommendation II.* Women diagnosed with hormone receptor–positive breast cancer who are postmenopausal should be offered adjuvant endocrine therapy with one of the following initial options:
- *Recommendation IIA.* Tamoxifen for a duration of 10 years.
- *Recommendation IIB.* An AI for a duration of 5 years. There are insufficient data currently to recommend an AI for a duration of greater than 5 years.
- *Recommendation IIC.* Tamoxifen for an initial duration of 5 years, then switching to an AI for up to 5 years, for a total duration of up to 10 years of adjuvant endocrine therapy.
- *Recommendation IID.* Tamoxifen for a duration of 2 to 3 years and switching to an AI for up to 5 years, for a total duration of up to 7 to 8 years of adjuvant endocrine therapy.

Appropriate Sequence of Adjuvant Endocrine Therapy

- *Recommendation III.* Women who are postmenopausal and are intolerant of either tamoxifen or an AI should be offered the alterna-tive type of adjuvant endocrine therapy.
- *Recommendation IIIA.* If women have received an AI but discontinued treatment at less than 5 years, they may be offered tamoxifen for a total of 5 years.
- *Recommendation IIIB.* If women have received tamoxifen for 2 to 3 years, they should be offered the option of switching to an AI for up to 5 years, for a total duration of up to 7 to 8 years of adjuvant endocrine therapy.
- *Recommendation IV.* Women who have received 5 years of tamoxifen as adjuvant endocrine therapy should be offered additional adjuvant endocrine treatment.
- *Recommendation IVA.* If women are postmenopausal, they should be offered continued tamoxifen for a total duration of 10 years or the option of switching to up to 5 years of an AI, for a total duration of up to 10 years of adjuvant endocrine therapy.
- *Recommendation IVB.* If women are pre- or perimenopausal, or menopausal status cannot be ascertained, they should be offered 5 additional years of tamoxifen, for a total of 10 years of adjuvant endocrine therapy.

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Surgery for Benign thyroid disorders

Chintamani

The most common presentation of benign thyroid disorders is in the form of nodular goiter which may be a solitary thyroid nodule or multi-nodular goiter. Palpable thyroid nodules may be detected in 0.8–1.5% of men and 5.3–6.4% of women [1,2] . Most of these nodules are benign colloid nodules composed of irregularly enlarged follicles containing abundant colloid. Most of the evidence in the management of benign in the management of benign nodular thyroid disease is grade C; only few studies have been rated grade A or B. The recommendations for the type and extent of surgery therefore would depend on the expertise of surgeon, center and the patient. The management being very subjective most surgeons tend to do the best in a given scenario and the minimum surgery offered is hemi-thyroidectomy and there are surgeons who would like to perform Total (TT) or Near Total Thyroidectomy (NTT) in any disease that is bilateral,

There are, however also surgeons who believe that since the natural history of benign goiter is usually slow growth of the nodules. Solitary nodules may disappear in 38% of all cases (grade C)*, therefore, observation can be safe*.

Solitary Thyroid Nodule

When it is decided to perform surgery Hemi-thyroidectomy (unilateral thyroid lobectomy+ isthumectomy) is the minimum surgery.

Indications for surgery in STN

The decision to operate or not may also depend on the reliability of diagnosis, the stability of the size of the nodule, the risk of subsequent dysfunction and the presence of other medical diseases.

- *A thyroid nodule which is larger than 3 cm, cystic/solid or large and cystic/solid may have a higher probability of malignancy (grade C), therefore it is recommended to perform surgery*. The intra-operative diagnosis by frozen section may be correct in 92% of cases [23]. Hemi-thyroidectomy is therefore the preferred therapy for patients with most benign solitary nodules(grade C).
- For the nodule with malignant or indeterminate cytology **hemi-thyroidectomy** is indicated as also in cysts that recur after aspiration

Surgery for MNG

Indications:

- If there is a suspicion of the nodules harboring cancer,
- Rapidly growing goiter
- If the large size is causing compressive symptoms, such as hoarseness, difficulty in swallowing, or in difficulty breathing.

N.B: 1.Use of thyroid hormone to attempt to "suppress" and shrink MNG is not indicated and puts patients at risk for hyperthyroidism.
2. "Radioactive Iodine ablation (RAI) may be an option in the treatment of MNG but is usually reserved for patients who are not fit for surgery due to co-morbid conditions".

It is commonly observed that there is no apparently normal thyroid tissue remaining especially in large bilateral MNGs making TT or the NTT as the only likely option. One therefore has to choose between leaving abnormal thyroid tissue behind or performing a total thyroidectomy. The former approach carries with it the risk of recurrent disease, which may require subsequent re-operation, whereas the latter approach theoretically has the potential hazards of an increased risk of either permanent hypo-parathyroidism or recurrent laryngeal nerve injury. The incidence of permanent complications after thyroidectomy, total thyroidectomy in particular, varies considerably from center to center. In experienced hands, however, the incidence is acceptably low; for example, Clark' reports an incidence of 1% permanent hypo-parathyroidism and no permanent recurrent laryngeal nerve damage in 82 consecutive total thyroidectomies. More than one-third of these were performed for benign thyroid disease. In 250 total thyroidectomies for nodular goiter, Perzik3 reported an incidence of only 0.4% nerve injury and no hypoparathyroidism. This contrasted with 5% nerve injury.

For the author, the NTT is the TT attempted but not achieved on scan or the Hartley Dunhill operation when while performing surgery on one side the parathyroids and/or the Recurrent laryngeal nerves and external laryngeal nerve cannot be seen, only a sleeve or a rim of tissue is left on the contralateral side preserving the recurrent laryngeal nerve and parathyroids .

Total thyroidectomy also has a very definitive role and is recommended for Graves' disease (especially in patients with severe ophthalmopathy), thyroiditis, and nodular goiter.

Sub total thyroidectomy

- It is no longer considered the optimum treatment especially when the entire gland is diseased in patients with MNG,
- Although it reduces the bulk of the diseased tissue. Leaving a small portion of diseased gland is unlikely to prevent the need for long-term thyroxine replacement therapy, whereas attempts to suppress regrowth of that remaining gland by thyroxine do not guarantee success.
- In performing a subtotal thyroidectomy it is also possible to leave behind the small posterior-lateral lobule of thyroid tissue that was first described by Zuckerkandl[2].
- This tissue often extends into the retro tracheal retro-esophageal area, causing significant pressure symptoms. The presence of this lobule is frequently only recognized when the full mobilization necessary for a total thyroidectomy has been performed.

Conclusions

1. Subtotal thyroidectomy in case of benign nodular thyroid disease is by far the most often used operation.
2. However, in recent years there is a trend for a more sophisticated surgical therapy, e.g., lobectomy plus contralateral subtotal lobectomy.
3. The significance of total thyroidectomy for benign nodular thyroid disease remains a subject of dispute unless clear evidence is present.
4. The identification of recurrent laryngeal nerve (RLN) and parathyroid glands is accepted by most authors.
5. Special surgical techniques, e.g., capsular dissection technique and neuro monitoring, may further improve the results of surgery and avoid complications. It is obvious that most evidence in benign thyroid disease is grade C.

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Radiological Evaluation of Intestinal Obstruction in Adults

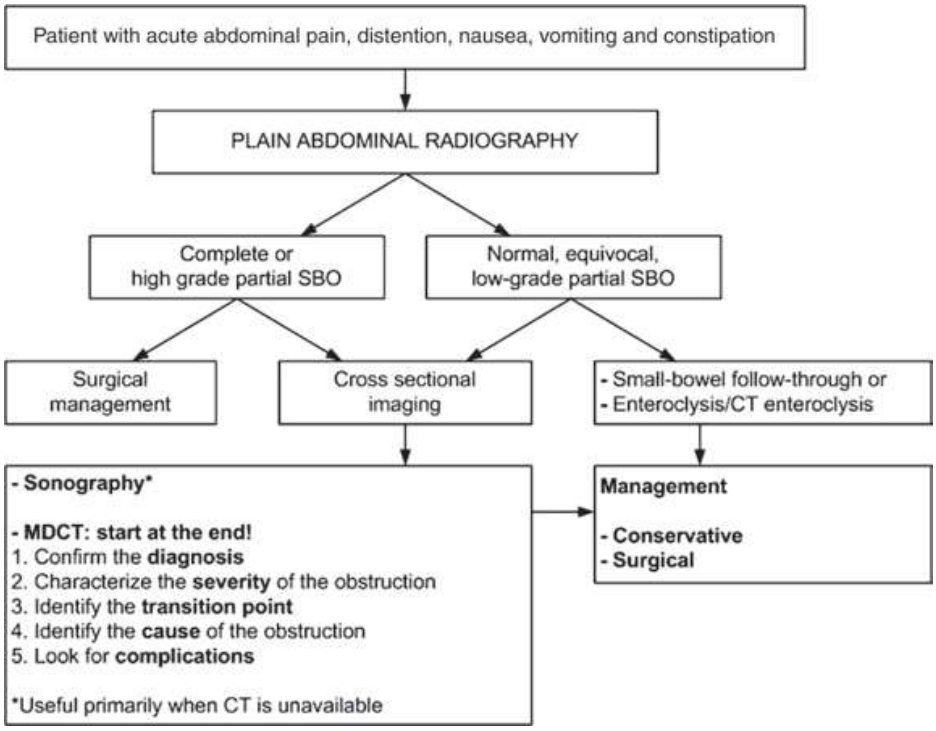
Anjali Prakash

SMALL BOWEL OBSTRUCTION

The radiological investigations of patients with SBO, the indications for and timing of surgical intervention have changed over past two decades. The old paradigm of 'never let the sun set or rise on an obstructed bowel' reflected the clinical and radiological limitations of preoperative recognition of strangulation. Nowadays imaging has become the primary focus, in the treatment of SBO. Radiology assumes relevance in assisting the surgeon in addressing the following questions

- **Is the small bowel obstructed?**
- **How severe is the obstruction?**
- **Where is it located?**
- **What is the cause?**
- **Is strangulation present?**

Various modalities are available to answer these questions and a suggested algorithm[1] is given in Fig 1.



Conventional radiography

- This is the preferred initial radiographic examination.
- Plain films are diagnostic in 50-60%, equivocal in 20-30% and normal, nonspecific, or misleading in 10-20%. The radiographs to be done are-

  1. **Supine abdomen** – bladder should be emptied before the film and film should include area from diaphragm to hernial orifices.
  2. **Chest radiographs**-
     - -superior to erect abdomen to detect pneumoperitoneum
     - -chest diseases may mimic SBO
     - -to serve as baseline
  3. **Erect abdomen**- air fluid levels are seen. Normal appearances- small amount of gas may be present. Two or more air fluid levels may be seen at D-J flexure and terminal ileum.

It is important to distinguish Large from Small bowel loops:

	Large Bowel	***Small Bowel***
Haustra	present	absent
Valvulae conniventes	absent	present in jejunum

Number of loops	few	many
Distribution of loops	peripheral	central
Radius of curvature of Loops	large	small
Diameter of loop	50 mm	30-50mm
Solid faeces	present	

Plain radiographic changes may appear after 3-5 hours, if there is complete small bowel obstruction and will be marked after 12 hrs. With incomplete obstruction, changes on plain radiograph may take days to appear.

The key radiographic signs that allow distinction between a high grade SBO and a low grade SBO are the presence of small bowel distention with maximal dilated loops averaging 36mm in diameter and exceeding 50% of caliber of largest visible colon loop. 2.5 times increase in number of distended loops in the abdomen compared with normal number. Other significant findings are the presence of more than two air fluid levels, air fluid levels wider than 2.5cm and levels differing more than 2cm in height from one another within the same bowel loop.

In dilated bowel loops, which are completely fluid filled, small bubbles of gas may be trapped in rows between valvulae conniventes on erect film, this is known as **'string of beads' sign**. This sign is virtually diagnostic of small bowel obstruction and indicates peristaltic hyperactivity to overcome mechanical obstruction. This is also seen sometimes in IBD or adynamic ileus.

X ray categories of SBO

- **Normal pattern** - absence of small bowel gas or small amount of gas within upto four non distended (less than 2.5cm) loops of small bowel. A normal distribution of gas and stool within a non distended colon should be visualized.
- **Abnormal but nonspecific gas pattern-** Atleast one loop of borderline or mildly distended small bowel (2.5-3cm) with three or more air fluid levels on erect film. The colonic gas and faeces distribution is normal or displays borderline distribution, this pattern is known as non specific
- **Probable SBO pattern**- abnormal gas distribution consisting of multiple gas or fluid filled loops of dilated small bowel with small/moderate amount of colonic gas.
- **Unequivocal SBO**- dilated gas or fluid filled small bowel loops in setting of gasless colon. This warrants immediate surgery.

In the patients with complete mechanical small bowel obstruction there is no gas in colon. This is a valuable differentiation between obstruction and adynamic ileus. Small amount of gas may be present in colon in early stages of SBO. Presence of colonic gas in later stages signifies putrefaction or iatrogenic cause. Large amount of colonic gas eliminates possibility of SBO.

Serial examination by plain radiography may be required in equivocal cases for analysis of position and amount of gas.

Causes of small bowel fluid levels-

- small bowel obstruction
- large bowel obstruction
- gastroenteritis
- hypokalemia
- uremia
- saline catharatics.
- cleansing enemas

Sonography: This is used when availability of CT is less. It is an operator dependent modality, with inherent ability in evaluating gas filled structures. At sonography bowel obstruction is considered to be present when lumen of fluid filled small bowel loop is dilated to more than 3cm. and the length of segment is more than 10cm, and peristalsis of dilated segment is increased as shown by to and fro or whirling motion of the bowel contents. This helps to differentiate a mechanical obstruction from adynamic ileus of peritonitis.

Level of obstruction may be determined by examining the area of transition from dilated to normal bowel. Causes of SBO like bezoars, intussception, crohns and tumor can be detected by this

method. Obstruction associated with external hernia is ideal for sonographic detection in that the dilated loop may be traced to a portion of gut in abnormal location.

The Severity of obstruction can be assessed by the presence of free fluid between dilated small bowel loops, aperistalsis and bowel wall thickening(>3mm) suggests bowel infaction.

Barium and water soluble contrast small bowel radiography: Water soluble contrast (eg urograffin) gets diluted and results in poor mucosal detail on radiography and is hypertonic. Hence it is not advisable and has shown to have no therapeutic effect in patient of SBO.

Oral barium is better as large amount of fluid in loop proximal to obstruction will dilute contrast and it will not inspissate and harden. Besides density is better with barium and chances of electrolyte imbalance are less. Before using barium in small bowel, colonic obstruction has to be excluded.

1. **Barium meal follow through**
   500ml of 42% w/v barium mixture is ingested, fluoroscopic $\pm$ overhead radiographs at 15-30 minute intervals, continue till ileocaecal valve, when barium has reached caecum, a rectal tube is inserted and air is insufflated to distend the right colon and barium filled distal small bowel.
   Advantages- patient preference, ease of administration and performance, ability to judge transit time.
   Disadvantages- length of examination, dilution of barium by gastric and intestinal contents, lack of complete distention of small bowel.

2. **Enteroclysis**
   The intubation and infusion of small bowel by barium, challenges the distensibility of bowel wall, exaggerating the effects of mild or subclinical obstruction. There is High sensitivity (100%) and specificity (88%) for SBO and high accuracy in determining the site and cause of obstruction. It also demonstrates acute angulation in patients with adhesions.
   Technique- infusion of 30-40% w/v barium suspension at 60-90 ml/min after duodenal intubation.
   Double contrast enteroclysis infusion of 60-95% w/v barium, followed by infusion of air/methyl cellulose to distend lumen leaving a thin coating of barium.
   Advantages of enteroclysis
   -shorter examination time
   -better distension
   -greater positive and negative for a wide range of SB pathology,
   including strictures, adhesions and intrinsic SB disease(eg sprue)

   Disadvantages
   -more radiologist time
   -patient discomfort

   Normal Luminal diameter of small bowel on barium examinations
- atleast $\leq$ 2.5cms
- distended after meal/SBFT
  - 3.5cm jejunum
  - 3cm ileum
- enteroclysis
  - 4.5cm upper jejunum
  - 4 cm jejunum
  - 3 cm ileum

3. **Capsule endoscopy** utilizes a small tablet size camera, that is swallowed by the patient, recording images of gut till expelled.
   Advantages- allows endoluminal views of areas beyond the reach of fibreoptic endoscopes
   Disadvantages- requires many hours of patient preparation
   -difficult to localise a pathological process that is visualized.

CT

Multidetector CT plays a primary role in evaluation of patients with SBO. It is a fast examination does not require oral contrast, as water serves as a great contrast, allows

assessment of bowel and extramural areas.The sensitivity of CT in detecting SBO ranges from 94-100%. For incomplete/intermittent obstruction CT combined with enteroclysis is the best method for evaluating the presence and degree of bowel obstruction.

CT criteria of SBO is the presence of dilated small bowel loops (diameter >2.5cms from outer wall to outer wall) proximally to normal caliber or collapsed loops distally.The transition point resembles a beak and is described as "**BEAK SIGN".**

How severe is the obstruction?

In high grade obstruction, there is 50% difference in caliber between the proximal dilated bowel and the distal collapsed bowel. The "**small bowel faeces sign**" is present when intraluminal particulate material is identified in the dilated small bowel. Its prevalence is low (7-8%) and is more likely to occur in high grade obstruction. It helps to locate the transition point. The transition point is determined by identifying a caliber change between dilated proximal and collapsed distal small bowel loop.

What is the cause of obstruction?

Most intrinsic bowel lesions are at the transition point and manifests as localized bowel wall thickening. Most extrinsic causes are adjacent to transition point and have associated extraluminal manifestation.

Is the SBO simple or complicated?

Simple obstruction of the bowel is considered when the bowel is occluded at one or several points along its course. The proximal part of bowel is distended, depending on severity and duration of the process.

Closed loop obstruction is diagnosed when a bowel loop of variable length is occluded at two adjacent points along its course. The CT signs of closed loop obstruction depend on length, degree of distension and orientation of the closed loop in the abdomen.

Characteristic fixed radial distribution of several dilated, usually fluid filled bowel loops with stretched and prominent mesenteric vessels converging towards point of torsion. The configuration may be C or U shaped, depending on orientation of loop. At the site of torsion of loop, a fusiform tapering may be seen 'beak sign'. Due to rotation of loops around a fixed point and volvulus a 'whirl sign' may be seen.

Strangulation is defined as a closed loop obstruction associated with intestinal ischemia. It complicates 10% of low grade and 40% of high grade SBO and occurs as a complication of intussception, torsion, volvulus or other forms of closed loop obstruction. Findings indicative of strangulation are thickening and increased attenuation of affected bowel wall. Abnormal bowel wall enhancement absent or poor contrast enhancement, portal or mesenteric venous gas/pneumatosis intestinalis- representing gangrene.

- Unusual mesenteric course- strangulated obstructions are associated torsion or twisting of bowel and mesenteric vessels, diffuse mesenteric vascular engorgement and haziness of mesentery is one of the most sensitive signs of strangulation. Bowel wall thickening may be seen and thickened bowel wall show target sign due to submucosal edema and hemorrhage.
- Serrated beak sign- is highly specific for strangulation. The U or C shaped configuration of dilated bowel loop with the ends of loop producing beak like narrowing with presence of mesenteric vascular engorgement.
- Ascitis- the presence of large amount of ascitis may point towards strangulation.

Findings of closed loop obstruction and strangulation on X ray-

- ***Coffee Bean sign***- the strangulated loop may contain gas and arms of the loop separated by thickened intestinal wall may resemble a large coffee bean.
- ***Pseudotumor sign***- the closed loop may fill with fluid and may be visible on a radiograph as a soft tissue mass or pseudotumor.

Findings on barium examination-

- Crossing defects obstructing two segments of a loop of bowel secondary to dense adhesions bands.
- Focal fixation of two limbs with intertwining of the involved limbs or twisting of the folds at point of obstruction suggestive of volvulus.
- Abdominal wall herniation with obstruction.
- Focal intraperitoneal segregation of a loop of bowel with tight obstruction suggestive of intestinal herniation.

MR Enteroclysis
New modality that provide adequate image quality and adequate distension of the small bowel. The inherent advantage being the potential to detect extraluminal pathologies and to provide detailed information about the wall of small bowel and the entire abdomen. It also does not use ionizing radiation.

Causes of SBO

Extrinsic

1. **Adhesions** are the main cause of SBO ranging from 50-80% of all causes. Almost all are post operative with a minority being secondary to peritonitis.

   The diagnosis of SBO due to adhesions is of exclusion because adhesion bands are not seen at CT, only an abrupt change in the caliber of bowel, without any associated mass lesion, significant inflammation or bowel wall thickening at the transition point. Adhesions are not seen CT even if multiplanar reformations are used; unless they are complicated by inflammation or carcinomatosis in which case they may appear as linear bands of soft tissue.
   Among adhesions, adhesive bands and malted adhesions can not be currently distinguished. Adhesive bands are usually constrictive and prone to high grade obstruction.

   Laproscopy is today indicated by some authors, in SBO from adhesive bands, it remains a contraindication in adhesive SBO from matted adhesion. In a recent report, a closed loop appearance on CT is the most sensitive sign of presence of adhesive bands. Other signs such as beak sign and fat notch sign which corresponds to extraluminal compression made by a band on the bowel at the transition zone, may be helpful in distinguishing the two causes.

2. **Hernias**
   - **Diagnosis of internal hernia is almost always radiological,** whereas external hernias is obvious at clinical examination. However USG or CT may be necessary in the following
     - to diagnose spigelian or obturator hernia in obese patient
     - inability to obtain good examination due to body habitus
     - to look for complications
   - **Paradoduodenal hernia**- are usually left sided and are believed to occur due to congenital defect in the descending mesocolon. They have a characteristic appearance of cluster of dilated small bowel loops, encased in a sac and lying between the pancreatic body and tail and stomach to the left of ligament of trietz. The herniated loops may become trapped within this mesenteric sac.
   - **Transmesenteric hernia**- when the small bowel herniates through a defect in the mesentry or omentum, the herniated bowel is compressed against the abdominal wall, with no overlying omental fat. The herniated bowel tends to appear clustered and lies inside of colon.

3. **Midgut volvulus**- malrotation of intestine results from normal embryologic sequence of the bowel development and fixation is interrupted. The malrotated bowel is prone to torsion, resulting in midgut volvulus. Malrotation results from incomplete rotation (<270 degree of counterclockwise rotation normally occurring in 5-12wks)

   This group of disorders can be divided into following categories-
   1. **nonrotation** (0 - <90 degrees of counterclockwise rotation occurring before 6wks)
   2. **reverse rotation** (abnormal rotation >90 and <180 degree causing obstruction or reversal of duodenal /SMA relationships occurring in 6-10wks)

3. **malrotation with malfixation** (>180 and <270 degree of counterclockwise occurring after 10wks)

Malrotation predisposes patients to two problems-

- midgut volvulus
- SBO

X ray findings

1. partial duodenal obstruction- dilatation of stomach and proximal duodenum with a small amount of distal gas.
2. gasless abdomen- features of SBO

Barium UGI

1. DJ flexure displaced downward and to the right.
2. abnormal position of jejunum lying to right of spine should alert one to the possibility of malrotation.

In malrotation with midgut volvulus

- dilated fluid filled duodenum
- proximal SBO
- a cockscrew pattern- proximal jejunum spiraling downwards in right or mid upper duodenum around its mesenteric axis.

USG - abnormal location of SMV to the left or posterior to SMA
- abnormal flow 'whirlpool sign' on Doppler shows mesentery and flow within SMV wrapping around SMA in a clockwise direction.

4. **Intussception**- uncommon cause of obstruction in adults.

X ray - dilated small bowel
- absence of caecal gas even in prone position

USG - Mass-loop within a loop appearance
-sandwich like appearance.

Barium enema-diagnostic

1. convex intraluminal filling defect-'claw sign'
2. coiled spring-contrast insinuates between the intussusceptum and intusscepien.

CT-

1. bowel within the bowel configuration
2. with or without mesenteric fat and vessels
3. a leading mass as cause may be identified

Intraluminal causes

1. **Gallstone ileus**- radiological triad of pneumobilia, ectopic gallstone and SBO.
2. **Bezoar** – SBO due to bezoar is rare, but due to bariatic surgery this has increased. This prevents adequate digestion of vegetable fibers which become impacted causing obstruction. At CT, a bezoar appears as an intraluminal mass with an ovoid shape and a mottled gas pattern.

Intrinsic

Small bowel neoplasms: Primary neoplastic causes of SBO are rare. Intrinsic small bowel neoplasia constitute less than 2% of GI malignancies. When a small bowel adenocarcinoma manifest as SBO, it is usually in an advanced state and shows pronounced asymmetric and irregular mural thickening (>4mm usually >1.5cms) with homogenous or heterogeneous enhancement, smooth, lobulated or irregular contour.

CT features of inflammatory or ischemic intestinal diseaseare different.they are circumferential, symmetric thickening of bowel wall <1.5cm, either segmental, diffuse and enhancing homogenously with i.v. contrast.

Small bowel involvement by metastatic cancer is more common than involvement than primary neoplasm. It is more frequent in form of peritoneal carcinomatosis, which is suggested when extensive serosal disease involving the small bowel is seen.

Tuberculosis Enteritis: In India, tuberculosis is a common cause of small bowel obstruction. The radiographic features of small bowel tuberculosis closely reflect the underlying pathological changes. The ulcerative form is most common,.the ulcers have stellate or linear shape.stellate ulcers are characterized by a barium speck with converging mucosal folds. linear ulcers are perpendicular to the long axis, resulting in spasm and circumferential strictures. Strictures are usually multiple and short. The hypertrophic form is less common, usually seen in ileocaecal area.the bowel loops are matted and fixed by adhesion and fibrosis.

Plain X-ray abdomen may show enteroliths with features of obstruction, i.e. dilated bowel loops with multiple air-fluid levels, evidence of ascitis, perforation or intussusceptions. In addition, there may be calcified lymph nodes, calcified granulomas and hepatosplenomegaly.

In all patients suspected of bowel tuberculosis, barium studies should include the barium meal follow through/enteroclysis followed by a barium enema, if there is a colonic involvement. The barium meal evaluates the motility and organic lesions in the terminal ileum and other parts of small bowel, while the per oral pneumocolon and enema, best evaluate the caecum and ileocaecal valve. Small bowel enteroclysis scores over cross sectional imaging and conventional intestinal studies in providing mucosal details and since this investigation requires adequate distension of intestine, early and incomplete strictures are better detected, as prestenotic dilatation develops at sites of minimal strictures.The radiographic features of intestinal tuberculosis have been correlated with the pathological state of disease.

First Stage: In this first stage of superficial invasion of the mucosa, radiological examination reveals:

a. An accelerated intestinal transit.
b. Disturbances in tone and peristaltic contractions resulting in hyper segmentation of the barium column, the so-called ‘chicken intestine’.
c. Disturbances in secretion, resulting in precipitation, flocculation or dilution of the barium suspension.
d. Changes in intestinal contours, which are irregular, crenated and interrupted by spiculae.
e. Changes in the mucosal pattern manifested by softened and thickened folds

Second Stage: The second stage, in addition to above comprise of ulcerations, characterised by a barium fleck surrounded by either a thickened wall or by converging folds.

Third Stage: The third stage is of sclerosis, hypertrophy and stenosis. In the small intestine penetrating ulcers cause very short ‘hour glass’ stenosis, that have smooth, but stiff contours and in which the mucosal relief has disappeared. Multiple strictures with segmental dilatation of bowel loops may occur. Other features include fixity of loops, spiculation, matting and signs of malabsorption).

Mucosal changes that occur in early stages of tuberculous enteritis are not usually sonographically visible. However, deep ulcerations can be detected and appear as radial extensions of the echogenic luminal contents into the surrounding thickened wall. With disease progression, wall thickening and short segment strictures develop in the intestine, resulting in partial intestinal obstruction and occasionally in intestinal perforations. On transverse sonograms, areas of narrowing representing strictures appear as segments of circumferential mural thickening and reduced luminal content. Real time sonography can assess hyperperistalsis proximal to the obstruction

Ileocaecal Tuberculosis: The ileocaecal region is most commonly affected in small bowel TB, because of physiological stasis, abundant lymphoid tissue, increased rate of absorption in the region and closer contact of the bacilli with the mucosa of the region.The lesion may be:

i. hyperplastic with long segments of narrowng, rigidity and loss of distensibility, i.e., the ‘pipe stem colon’, which is the commonest,
ii. ulcerative
iii. ulcerohyperplastic and
iv. Carcinoma type with a short annular defect and overhanging edges.

Early involvement of the ileocaecal region is manifest as spasm and hypermotility with edema of the valve. Thickening of the ileocaecal valve lips and/or wide gaping of the valve, with narrowing of the terminal ileum (the ‘Fleischner or inverted umbrella’ sign) are considered

characteristic of tuberculosis. In advanced disease, the characteristic deformity includes symmetric, annular, 'napkin ring' stenosis and obstruction or shortening, retraction and pouch formation. The caecum classically becomes conical, shrunken and retracted out of the iliac fossa due to contraction of the mesocolon. Hepatic flexure may also be pulled down. There may be loss of the normal ileocaecal angle and the dilated terminal ileum may appear suspended and hanging from a retracted, shortened caecum (goose neck deformity) Localised partial stenosis opposite the ileocaecal value with a rounded off smooth caecum and a dilated terminal ileum resembles a purse string stenosis. The ileocaecal value becomes fixed, irregular, gaping and incompetent. The terminal ileum may be fixed and narrowed due to stricture formation. Narrowing of the terminal ileum may occur due to irritability with rapid emptying through a gaping ileocaecal value with a shortened, rigid or obliterated caecum "Stierlin's sign". This represents acute inflammation superimposed on a chronically involved segment of the ileum, caecum or ascending colon with a normal configured column of barium on either side. A persistent narrow stream of barium in the bowel indicates stenosis and is known as the 'string sign'.Both Stierlin's sign and string sign are also noted in Crohn's disease and cannot be considered specific for tuberculosis. Hyperplastic tuberculosis mimics carcinoma and histological diagnosis is mandatory.

Sonography shows extramucosal changes and can occasionally detect mucosal changes. In early stages of ileocaecal tuberculosis, a few regional nodes and circumferential thickening of the wall of the caecum and terminal ileum may be visualised. The bowel wall is considered thickened when it measures > 5 mm in the small bowel when non-distended, and > 3 mm when distended. In later stages of disease, the ileocaecal value and adjacent medial wall of the caecum are predominantly and asymmetrically thickened. These changes are nonspecific and may be seen in other conditions such as carcinoma, Crohn's disease, lymphoma and amoebiasis. However, in Crohn's disease eccentric thickening may be noted at mesenteric border and a variegated appearance is seen in malignancy. Due to the predilection for TB of the ileocaecal region and the tendency of the ileocaecal region to be pulled upto a subhepatic position, a pseudo-kidney sign seen in this location is highly suggestive of a tuberculous pathology. In advanced ileocaecal tuberculosis, gross wall thickening, adherent loops, large regional nodes and mesenteric thickening may together form a complex mass of varied echogenicity centered on the ileocaecal regionThese changes are highly suggestive of tuberculosis in the appropriate clinical setting. Ultrasound can detect ulcerations, however due to associated spasm, there is low sensitivity of the same. Lesions in jejunum or proximal ileum can be missed due to difficulty in scanning the entire length of the intestines, and is also limited by presence of overlying bowel gas.

CT scans of the ileocaecal region, may show circumferential bowel wall thickening up to 3.0 cm in diameter in terminal ileum and caecum with enlargement of ileocaecal valve and adjacent mesenteric adenopathyThe bowel wall thickening may be mild and symmetric or severe and asymmetric with a homogeneous density and areas of slight heterogeneous appearance. A CT appearance more characteristic of TB is asymmetric thickening of the ileocaecal valve and medial wall of the caecum with an exophytic extension engulfing the terminal ileum and massive lymphadenopathy with central low attenuation area. Pericaecal or mesenteric fat shows either absence or only minimal haziness. CT may also show distal small bowel obstruction.

CT enteroclysis has a greater sensitivity and specificity than nonhelical CT in patients suspected of having low grade small bowel obstruction, a feature commonly seen in small bowel tb.CT enteroclysis allows detection of luminal and extraluminal disease.

Radiological differentiation of early stage ileocaecal tuberculosis from Crohn's disease and lymphoma is usually impossible. CT is capable of identifying changes in bowel wall and mesentery to provide differentiating factors between advanced intestinal tuberculosis and Crohn's disease. In tuberculosis, bowel wall changes are varied and reflect the various stages of the disease. These are exophytic soft tissue masses surrounding a constricted and ulcerated lumen, minimal but asymmetrical bowel wall thickening with spiky or tethered mucosal outline, minimal symmetrical wall thickening and absence of wall

thickening. Mucosal stratification does not occur. In comparison, Crohn's disease has a uniform pattern of wall thickening, which is concentric or largely symmetrical, ranging from 0.6 to 1.7 cm, few showing mural stratification. Although amebiasis may produce the typical shrunken caecum seen in TB, associated small bowel involvement is rare. Caecal malignancy is always limited by the ileocaecal valve

The differentiating imaging features of ileocaecal involvement can be summarized as :

	TUBERCULOSIS	CROHN'S DISEASE
1.	Asymmetric wall thickening, irregular	Circumferential bowel wall thickening
2.	Fleischner sign on barium studies	Cobblestone appearance on barium
3.	No creeping fat	Creeping fat (abnormal quantity of mesenteric fat) present
4.	Positive chest film (50%)	Negative chest film
5.	Omental and peritoneal thickening	Normal omentum and peritoneum
6.	Enlarged lymph nodes with low-density centers	Enlarged soft-tissue density lymph nodes

Colonic Tuberculosis: The large bowel is involved in 9 per cent of cases without small bowel involvement. Colonic disease may present as a segmental involvement (long or short) with spiculation, spasm, rigidity and ulceration. Occasionally, inflammatory polyps, perforations and fistulae may occur with pericolic abscesses. The differential diagnosis of extensive colonic tuberculosis include ulcerative colitis, Crohn's disease, amoebic colitis, ischemic and pseudomembranous colitis, as well as malignancy. Anal involvement and internal fistulae are more common in Crohn's disease while free perforation is more common in TB. The ulceration in TB is circumferential while that in Crohn's disease is along the mesenteric border .

Enterolithiasis

Intestinal calculi may form above any bowel stricture. When the stricture is high in the small bowel, the enteroliths are usually nonopaque, being composed of choleic acid. In the lower small bowel, due to a more alkaline medium and a higher concentration of calcium salts, enteroliths are often opaque. They may be completely opacified or have translucent centres with a ring of calcification. They vary from being multiple, small stones to a large lamellated calculus and must be differentiated from renal stones, gallstones, vesical stones and calcified granulomas

LARGE BOWEL OBSTRUCTION

Causes

1. The commonest Cause of large bowel obstruction is carcinoma. 60% situated in Sigmoid Colon.
2. Diverticular disease
3. Volvulus of colon
4. Hernia.

Three patterns of large bowel obstruction have been defined.

Type 1A: Ileocaecal valve is competent. Dilated colon with distended thin walled caecum , but no distension of small bowel is seen.

Type 1B: Progression of 1A results in increasing small bowel distension. Both types can lead to massive caecal distension, which is then at risk of perforation secondary to ischemia. A transverse caecal diameter of 9cm is critical above which the danger of perforation.

Type 2: Ileocaecal valve is incompetent. Caecum & ascending colon are not dilated, but backpressure results in numerous dilated loops of small bowel.

Plain X Ray

- The obstructed colon contains large amount of air, identified as by its haustral margin around periphery of abdomen.

- When both small and large bowel dilatation is present, differential diagnosis includes paralytic ileus. A left lateral radiograph will demonstrate air in rectum in paralytic ileus.
- There are many causes of colonic distension without obstruction, including paralytic ileus & pseudo obstruction. Prior to surgery, a single contrast dilute barium enema /CT should be done to confirm mechanical obstruction.

Advantage of Double Contrast Barium Enema over Single Contrast BE
- Detection of Small polyps
- Detection of superficial ulceration.

Advantage of single contrast BE
- Patient Comfort
- Elderly/arthritic patient
- Detection of strictures
- Detection of large masses
- Evaluation of obstruction

Indication for water soluble contrast enema
- Possible perforation
- Fistula?
- Pre operative emergent study
- Therapeutic

How do you distinguish various causes of colonic luminal narrowing?
- Benign stricture – smooth tapering at both ends.
- Malignant stricture- Irregular, abrupt narrowing, apple core, shoulders at one or both ends.
- Extrinsic- Intact mucosa, whole lumen is displaced, oblique angles for mass effect.
- Submucosal intact mucosa, almost right angle interface with luminal surface.
- Mucosal- Irregular mucosal surface acute angle interface with luminal surface.

Virtual Colonoscopy—CT colonography

It entails cleaning the patients bowel by as colonoscopy preparation, insufflation of room air into the cleansed colon with a rectal enema catheter and thin section helical CT of the abdomen & pelvis followed by off line computerized manipulation of the CT data to generate an endoscopic view of colonic mucosa.

Virtual colonoscopy plays an important role in the diagnosis of distal occlusive carcinoma, which are defined as lumen that cannot be harvested endoscopically.

It can demonstrate the entire colon in majority of patients and ia accurate in depicting synchronous colorectal malignancy. Pre operative Barium enema examination in these patients is technically difficult, is associated with an increased risk of barium inspissation and may necessitate a delay before surgery to adequately clean the bowel.
By reference to adjacent osseous and soft tissue landmarks an axial CT images and multiplanar reconstruction, it is possible to predict tumour location more accurately at virtual colonoscopy than at conventional colonoscopy. This may influence surgical conduct such as location of incision, level of placement of epidural cathetar, extent of resection and stomal site planning.

Colorectal cancer: Colorectal tumors are the main cause of large bowel obstruction. Most of these tumors are Adenocarcinoma and cause obstruction by luminal compromise & bowel wall thickening. Colonic tumours may invade the mesentry and small bowel with concomitant small bowel obstruction. Barium enema detects approx 85% of colorectal cancers.poor distension,inadequate coating or overlapping loops may impair interpretation.CT is a viable alternative in frail and elderly patients in whom barium enema is technically difficult.Luminal narrowing is short (<10 cm), abrupt, irregular and eccentric may resemble apple core.CTis used for staging. CT also aids in staging the malignancy The entire colon needs to be evaluated for synchronus lesions.CT can also be used for follow up,every six months for 2-3 years ,then annually for 5 years. PET-CT can be used for recurrence and surveillance.

Large Bowel Volvulus: Torsion of colon can occur in only those parts which have a long, freely mobile mesentry. This is commonest in sigmoid colon. Occasionly caecum and ascending colon

may be involved. Compound volvulus involving intertwining of two loops of bowel as ileosigmoid knot.

Caecal Volvulus: Caecal volvulus can only occur when the caecum & ascending colon are on a mesentry and this is associated with a degree of malrotation. This accounts for <2% of all cases. Age Group 30 – 60 years.

Radiological Finding: In about half the patients, the caecum twists and inverts so that the pole of caecum and appendix occupy left upper quadrant. In other half it twists in an axial plane without inversion and then the caecum occupies the right half or central half of abdomen.

- Distended caecum is seen as large gas filled viscus.
- One or two Haustral Markings are identified.
- Identification of attached gas filled appendix.
- Moderate SBO with left half of colon is collapsed.

Sigmoid Volvulus: This occurs in elderly, mentally retarded and instutionalised patients. The usual Mechanism is twisting of sigmoid loop around its mesenteric axis. Sigmoid volvulus is usually chronic, with intermittent acute attacks. The main problem lies in distinguishing a twisted sigmoid from a distended but nonrotated sigmoid or distended transverse colon looping down into the pelvis (Pseudovolvulus).

Plain X-Ray

1. An inverted U shaped loop is seen , which is markedly distended & commonly devoid of haustria /ahaustrial.
2. The ahustial margin can be identified overlapping the lower border of liver shadow (LIVER OVERLAP SIGN)
3. It may overlie Haustrated dilated desending colon. Left flank Overlap sign and left side of pelvis. (PELVIS OVERLAP SIGN)
4. The apex of volvulus lies high in abdomen under the left hemidiaphragm with apex at or above level of D10.
5. Inferiorly, where the two limbs of loop converge, three white lines representing thr two outer walls and the adjacent inner walls of the twisted loop meet. This is called inferior convergence. It is usually on the left side of the pelvis at the level of upper sacral segment.
6. Large amount of air is present in sigmoid volvulus and an air fluid ratio of >2:1 is usual.

The left Flank overlap, apex under left hemidiaphragm & inferior convergence sign are highly specific and sensitive.

Barium Enema

1. A smooth curved tapering of the barium column like a hooked beak is seen at point of torsion (Bird of prey sign)
2. Mucosal fold show a cork screw pattern at point of twist.

Pseudoobstruction/ Ogilvie's Syndrome: This is a clinical condition that presents with large bowel obstruction without any evidence of mechanical obstruction. The colon may become massively dilated and if not decompressed, there is a risk of perforation with peritonitis. This is thought to be due to imbalance in autonomic innervation that leads to a functional large bowel obstruction. When this condition is acquired, acute or coexisting with other medical condition, it is called Ogilvie's syndrome. Radiological diagnosis is of exclusion. There is marked dilatation of entire colon with faecal loading in the absence of any obstructive lesion.

Adynamic Ileus: This is a common disorder of intestinal motor activity in which fluid & gas do not progress normally through a nonobstructed small & large bowel. Clinically, patient may have minimal symptoms to generalized abdominal distension, with a marked decrease in frequency & intensity of bowel sounds.

The radiographic hallmark of adynamic ileus is retention of large amount of gas & fluid in a demonstrable point of obstruction. Concomitant distension of the gas filled stomach, an uncommon occurrence with mechanical small bowel obstruction, is often seen in patients with adynamic ileus (especially when it is secondary to peritonitis)

Adynamic ileus may be seen in postop cases, peritonitis, secondary to electrolyte imbalance, metabolic disorder, trauma, acute chest disease.

Localised Ileus: An isolated distended loop of small or large bowel reflecting a localized adynamic ileus(sentinal loop) is often associated with an adjacent acute inflammatory process eg- localized segment of jejunum or transverse colon are frequently dilated in pancreatitis.

Pnemoperitonium without peritonitis

1. Post operative
2. Dialysis
3. Laproscopy
4. Silent healed perforation
5. Association with chest condition- pneumonia, emphysema,IPP.

Use of contrast media in suspected perforation: In equivocal cases

1. 100 ml of air injected through NG tube and further film taken after patient lies in left lateral position for 10 minutes.
2. 50 ml of water soluble contrast like Urograffin given orally, patient placed right side for 5 min &hen examine under fluoroscopy.
3. CT can be done.

Pneumoperitonium: As little as 1ml of free air can be demonstrated radiographically on erect chest or left lateral decubitus abdominal films. Patient should be in this position for at least 10 min to enable air to rise to highest position.On the left side, free air may be difficult to distinguish from gastric or colonic air. A left lateral radiograph helps by demonstrating gas between liver and abdominal wall.

Sign of pneumoperitonium on supine radiograph:

- Right upper quadrant gas- perihepatic, subhepatic.
- Riglers sign- visualization of outer & inner wall of bowel
- Ligament visualization
  - Falciform- ligamentum teres
  - Umbilical inverted V sign- Medial & lateral
  - Urachus
- Triangular air collection
- Cupola sign
- Football sign

Pseudo Pneumoperitonium -- These mimic free air.

- Chilaiditi syndrome—Interposition of bowel between liver and diaphragm on the right side may simulate pneumoperitonium.
- Subdiaphragmatic fat
- Curvilinear supra diaphragmatic pulmonary collapse
- Subphrenic absess
- Intramural gas as in pneumotosis intestinals.

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Asymptomatic skeletal metastases

Ravi Kannan, Ritesh Tapkire, Mira Wagh

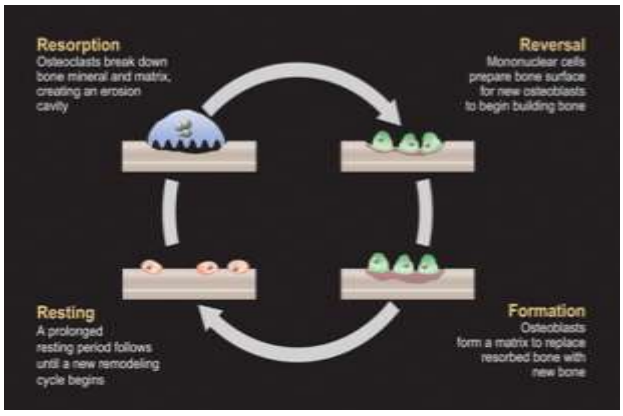
Introduction

All malignancies can metastasise to bone and these are usually multiple and are often associated with visceral metastases. Bone is the third most common organ affected by metastasis, after the lungs and the liver. Breast and lung in women and prostate and lung in men are the commonest primary cancers metastasising to bone. Other frequent primary sites include kidney and thyroid. Breast and prostate cancers metastasize to bone more frequently, because of the high incidence and prolonged clinical course of these malignancies. An estimated 70% of patients with breast and prostate cancers develop bone metastases compared with 20% to 30% of patients with lung or gastrointestinal cancers (1).

Asymptomatic skeletal secondaries are diagnosed in two situations 1.during staging work up for a known cancer; 2. As a diagnostic dilemma when a bony lesion is detected incidentally during investigations for an unrelated problem. In any individual over the age of 40 years, a bony lesion is 500 times more likely to be a metastatic lesion than a primary – more so if there is a known primary cancer. Lesions at unusual sites and unusual presentations are more likely to be metastatic. Single site metastatic lesions occur about 25% of the time. The location of the lesion gives a clue about the possible primary (2). Acral metastases below the knee or elbow are more likely to be from lung primaries. Sternal lesions often indicate haematological disease. Lesions around the shoulder after 30 years of age could indicate myeloma or lymphoma. Symmetrical metastases could indicate a rhabdomyosacoma. 'Head less' bone scans would indicate a prostate primary.

Physiology of turnover of normal bone (3, 4)

Normal bone is in a dynamic balance between the activities of osteoblasts and osteoclasts throughout an individuals life. Osteoblasts synthesise osteoid (collagen and other bone proteins and ground substance including chondroitin sulphate and osteocalcin) and are involved in mineralization of the bone matrix. Normal bone remodeling consists of continuous resorption of mineralized matrix coupled with the subsequent replacement of lost bone at numerous skeletal sites. (Figure 1.)



Remodeling is initiated by focal attraction of osteoclasts to a locus on the bone surface (activation) where they break down the bone mineral and matrix, creating irregular erosion cavities (resorption). Mononuclear cells then smoothen the erosion cavities (reversal). Osteoblasts are now attracted to the to the eroded surface (coupling) where they synthesise an osteoid matrix. The newly formed osteoid undergoes mineralization. The delay between matrix synthesis and mineralization accounts for the appearance of osteoid (which makes up 50% of bone volume and 40% of bone weight) in normal bone. During this period osteoid incorporates other bone proteins and matures. Under normal physiologic conditions, the amount of new calcified matrix that is produced by the osteoblast is equal to the amount of bone resorbed by the osteoclast (3).

Both systemic and local factors influence bone remodeling. Estrogen (and androgens through aromatisation to estrogen in bone) is the key hormone for maintaining bone mass. Age-related bone

loss in both sexes is largely due to estrogen deficiency. Estrogen (4a) decreases the formation, activation, and life span of osteoclasts. There is some evidence that suggests that estrogen increases osteoblast formation, differentiation, proliferation, and function. Loss of estrogen due to any cause results in increased volume of the resorption cavity that is beyond the capacity of the osteoblasts to refill.

Osteoblasts are derived from mesenchymal stem cells while osteoclasts are of haematopoetic stem cell lineage. Receptor activator of nuclear factor-κB ligand (RANKL), an essential cytokine for the formation and activation of osteoclasts, is expressed on the surface of osteoblasts. RANKL binds to and activates the RANK receptor expressed on osteoclasts and osteoclast precursor cells (5). It is a potent inducer of osteoclast formation and promotes its survival. 1,25-dihydroxyvitamin D3, parathyroid hormone, prostaglandin E2, and interleukin 11 induce the formation of osteoclasts by up-regulating RANKL expression on the surface of marrow stromal cells and immature osteoblasts. A decoy receptor, osteoprotegerin OPG, also secreted by the stromal-osteoblast lineage inhibits RANKL by binding to it. (Figure 2). In addition, co-expression of RANKL and vascular endothelial growth factor by malignant B-lymphoid cells and other tumors may contribute to the close cellular interactions with osteoclasts to enhance bone destruction and tumor expansion in bone.

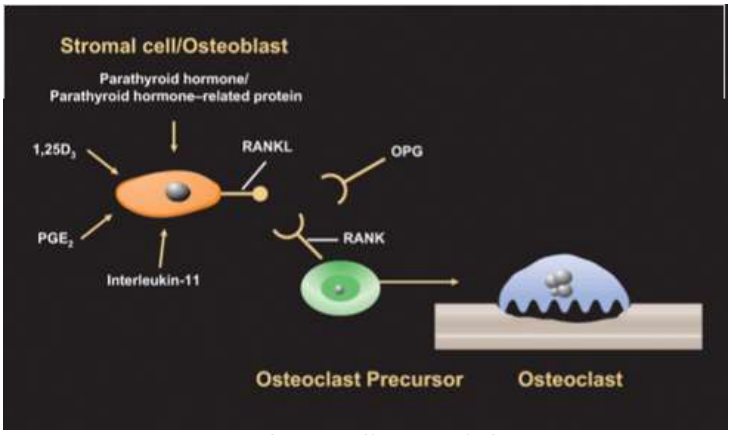


Figure 2.(from Ref.3)

Pathophysiology of bone metastases

Historically, Batson described the high flow, low-pressure, valveless plexus of veins that connects the visceral organs to the spine and pelvis.1 Recent research has focused on the multistep cellular process of metastases. First, the cancer cell must disengage from its primary site. The loss of expression of E-cadherin, a cell surface adhesion molecule, has been demonstrated in breast, prostate, colorectal, and pancreatic carcinoma as an early step in cellular disengagement. After invasion of the vascular or lymphatic system, the cancer cell must survive the immune system and then arrest at its final destination. At the distant site, the malignant cell must adhere to the basement membrane, invade the surrounding tissue, induce angiogenesis, and develop into a secondary mass. Cell adhesion molecules from the integrin family, immunoglobulin superfamily (intracellular adhesion molecule, vascular cell adhesion molecule, and platelet endothelial cell adhesion molecule), and selectin family of receptors have been implicated in adhesion to basement membrane proteins such as laminin at the target site.5 After tissue invasion, angiogenesis is required for continued tumor growth

Physiology of Bone Turnover in Skeletal Metastases (3,4,6)

Skeletal metastases may be osteolytic or osteoblastic that represents extremes of a spectrum of abnormal bone remodeling. Patients may have mixed patterns having both elements.

Osteolytic lesions on x-ray films are characterized by increased bone resorption with less bone formation and are commonly seen in lung, renal, and breast cancer. The bone destruction is mediated by osteoclasts which are activated by tumour derived factors that impact on the RANKL system. These include IL-6, IL-8, and IL-11, tumour necrosis factor (TNF), macrophage colony-stimulating factor (M CSF), prostaglandin E2, and PTH-RP. IL8 might also have effects on the osteoclasts

independent of the RANKL pathway. Tumour cells might contribute to bone destruction by compression of vasculature resulting in ischemic necrosis. In addition,the process of bone resorption itself results in the release of tumour growth factors from the bone matrix, including transforming growth factor beta (TGF-beta), insulin-like growth factors, fibroblast growth factors, platelet-derived growth factor, and bone morphogenetic proteins. TGF-beta in turn stimulates production of osteolytic factors such as PTH-RP, IL-11, and prometastatic factors such as connective tissue growth factors. This results in a vicious cycle of tumor growth and bone destruction. (Figure 3).

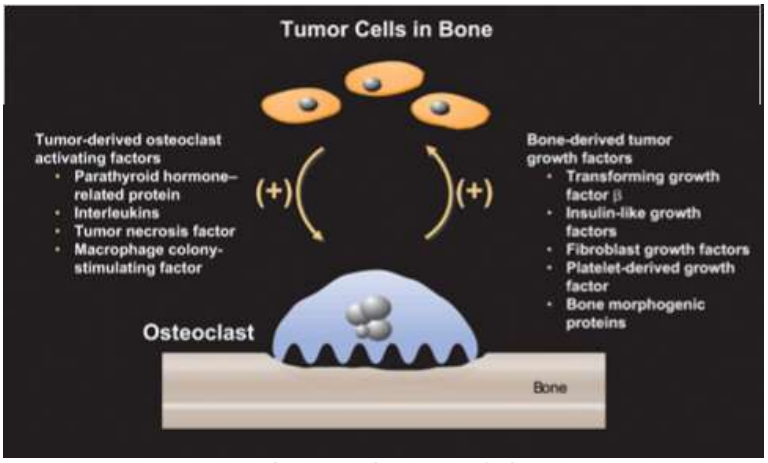


Figure 3. (From Ref 6)

Bone lesions in myeloma (4) are purely osteolytic caused by heightened activity of osteoclasts stimulated by large amounts of macrophage inflammatory protein-1 alpha, as well as IL-1, IL-3and IL-6 secreted by the tumour cells. Macrophage inflammatory protein-1 alpha also enhances adhesive interactions between myeloma cells, which stimulates production of RANKL and IL-6 by the stromal cells/ osteoblasts. Enhanced expression of RANKL and diminished production of OPG contribute to the increased osteoclastic bone destruction. The suppression of osteoblast activity in myeloma may be due to production of Dickkopf-1 (DKK1) (an inhibitor of osteoblasts) by myeloma cells. (Figure 4).

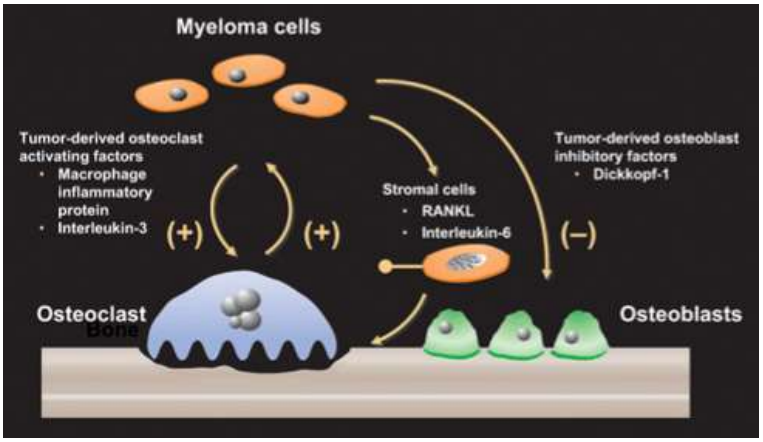


Figure 4. (From Ref.6)

Osteoblastic (7) bone metastases appear sclerotic on x-ray films, are characterised by increased bone formation. These are most commonly seen in patients with prostate cancer. About 40% of lymphoma metastases and 10% of breast cancer metastases are osteoblastic. Tumor cells produce endothelin-1 and other factors, which stimulate osteoblasts to a) cause abnormal bone formation. and b) release tumour growth factors. Osteoblastic metastatic tumor cells also release growth factors, such as PTH-RP and IL-6, TGF-beta, and bone morphogenetic proteins, that stimulate osteoclastic recruitment and differentiation. In turn, osteoclastic activity leads to the release of growth factors that also stimulate tumor cell growth. (Figure 5).

Metabolites of bone turnover may be measured in the serum or urine as indicators of normal and pathologic bone turnover (8). During bone formation, markers released into the circulation include bone-specific alkaline phosphatase (ALP), procollagen extension peptides, and osteocalcin (OC). Collagen breakdown during bone resorbtion results in the release of N-telopeptide cross-links (NTx),

C-telopeptide cross-links (Ctx), pyridinoline (Pyr), and deoxypyridinoline (DPD) into the circulation. These markers can be elevated in bone metastases or in other conditions in which bone turnover is high, such as bone loss related to cancer treatment but are rarely used clinically.

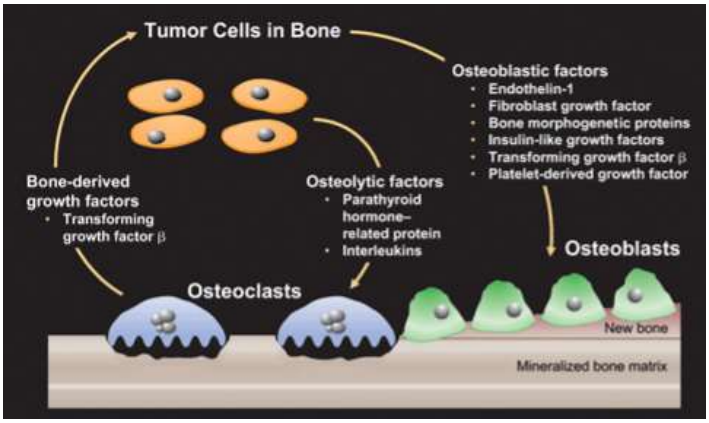


Figure 5. (From Ref.6)

Clinical course of skeletal metastases (9)

The prevalence of metastatic bone disease is highest in breast and prostate cancer; these 2 primary tumor types account for approximately 80% of all cases of metastatic bone disease. 65%-75% of patients with advanced breast and prostate cancer develop bone metastases; approximately 40% of patients with advanced lung cancer develop bone metastases.

Survival prospects after metastases to bone vary greatly depending on tumor type and sites of involvement. Mean survival ranges from a low of 6 months, for those with lung carcinoma, to several years for subjects with bone metastases from prostate, thyroid, or breast carcinoma. If patients have only skeletal metastases, their average survival is longer. With prolongation in survival, the main challenge is to improve the quality of the patient's remaining life. The morbidity associated with metastatic bone disease, often referred to as skeletal-related events or SREs, includes pain that may require opiates, the need for radiotherapy and/or surgery, hypercalcemia, pathologic fractures, and spinal cord compression.

Lesions in patients with breast cancer are mainly osteolytic in appearance. About one third of patients present with mixed osteoblastic and osteolytic features while 10% have pure osteoblastic deposits on plain x-rays. Bone metastases in patients with prostate cancer are typically osteoblastic in appearance. The incidence of bone metastases at diagnosis is influenced by clinical stage, histologic grade, and serum prostate-specific antigen levels. Two-thirds of patients with high grade prostate cancer develop osseous metastases at 15 years. The extent of osseous involvement directly correlates with patient survival. Non-small cell lung cancer (NSCLC) comprises the majority (75%–80%) of all lung cancers. 11% to 36% of patients present with distant metastases, frequently involving bone. Bone metastases are typically osteolytic. Combination chemotherapy has increased the median survival of these patients to 8-10 months. More than a third of these patients live for a year. 17-50% of all newly diagnosed renal cell carcinomas have skeletal metastases. While they are typically osteolytic, mixed or pure osteoblastic lesions can also happen. Lesions predominantly affect the axial skeleton and are hypervascular. Median time from diagnosis of RCC to appearance of skeleton is about 14 months while the median survival time for patients with metastatic RCC is only 6 to 12 months. Many of the major clinical manifestations of multiple myeloma (MM) are related to osteolytic bone destruction. 23% of patients have osteoporosis while 67% have osteolytic lesions at diagnosis. Skeletal lesions developed in 84% of patients during their disease. The median survival of these patients is 33 months.

Bone metastases, if untreated, can cause substantial skeletal morbidity, including bone pain, impaired mobility, hypercalcemia, pathologic fracture, spinal cord or nerve root compression, and bone marrow infiltration. When these skeletal-related events (SREs) are considered across all tumor types, patients with breast cancer are found to have the highest incidence of skeletal complications. Approximately 70% of patients with breast cancer treated with placebo experienced at least 1 skeletal complication

during a 2-year follow-up period. Patients with myeloma, prostate cancer, and lung cancer are also at high risk of skeletal complications. Approximately 50% of patients with these tumor types experience an SRE during a 21- to 24-month period. The most common events in all tumor types are radiation to bone and pathologic fracture.

Imaging (2)
Asymptomatic bone lesions are discovered during staging investigations or incidentally during investigations for a malignant or benign pathology. Investigations include plain x-rays, CT or MRI scans, radionuclide imaging -Tc99m bone scans, SPECT or PET scans. Currently Tc99m bone scintigraphy is often the first investigation for screening the bone. This is likely to change with greater availability of PET CT machines and reduction in costs of the investigation.

Other than for myeloma, plain x-rays cannot be recommended for screening for asymptomatic bone metastases. Compared with other imaging techniques, radiography is relatively insensitive in detecting bone metastases, especially subtle lesions. As a general rule, only lesions 2 cm or larger are radiographically apparent. Metastases to bone become apparent on radiographs only after the loss of more than 50% of the bone mineral content at the site of disease. It is important to note that unlike primary bone tumours, in general metastases incite no or only limited periosteal reaction. The occasional exception to this general rule includes prostate cancer, some gastrointestinal malignancies, retinoblastoma and neuroblastoma [3].

Screening for asymptomatic bone metastases is not recommended for early cancers since it does not confer any survival advantage (10). In patients with breast cancer, bone/ PET scans are recommended only for stage IIIa (T3N1) and above. Imaging for lower stages is recommended only if the patient is symptomatic or serum alkaline phosphatase is elevated. All symptomatic prostate cancer patients and asymptomatic patients who expect to be alive for 5 years will undergo a bone scan. Patients with high grade tumours (Gleason's grade>/= 8) and those with serum PSA> 20 ng/ml also should have a bone scan even if asymptomatic. Bone scans are also indicated in post prostatectomy patients who have a rising PSA but are other wise asymptomatic.

Skeletal imaging/ bone scans are indicated only in symptomatic (for bone) patients with RCC. Most patients with lung cancer will undergo a PET CT to stage the mediastinum. Bone scans are not indicated in MM. Plain x-ray skeletal survey suffices. Four distinct x-ray patterns of involvement have been described: the solitary lesion (plasmacytoma), diffuse skeletal involvement, diffuse skeletal osteopenia, and sclerosing myeloma. In certain situations a PET CT or MRI may be necessary.

Technetium-99 (99mTc) bone scintigraphy is a nuclear imaging study that is sensitive for identifying osseous metastases regardless of symptoms. Indications for bone scintiscanning include staging in asymptomatic patients, evaluating persistent pain in the presence of equivocal or negative radiographic findings, determining the extent of bone metastases in patients with positive radiograph findings, differentiating metastatic from traumatic fractures by assessing the pattern of involvement, and determining the therapeutic response to metastases. It provides total skeletal examination, has a relative low cost, and thus is often the initial imaging modality for detection of bone metastases. 99mTc bone scintiscan findings are nonspecific in determining the cause of increased uptake, particularly in solitary lesions.

99mTc shows an osteoblastic bone reaction by accumulating in reactive bones, where an elevated rate of bone turnover occurs. However, 99mTc bone scan cannot detect pure osteolytic metastases, and the poor specificity of this scan as well as its lack of anatomic detail often require that anatomic imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) be obtained for further characterization. Single-photon emission computed tomography (SPECT) improves the sensitivity and specificity of 99mTc bone scans for detection of small bone metastases, but its use has largely been replaced by the wide availability of MRI, which provides a superior quality tomographic image.

False-negative bone scans are also possible for highly aggressive and rapidly growing lytic tumors because of minimal reactive bone formation; these tumors are better detected by metabolic scans such as fluorodeoxyglucose-positron emission tomography (FDG-PET) because they have a high glucose metabolism PET scanning can help in identifying bone metastases at an early stage of growth, before host reactions to the osteoblasts occur. FDG-PET scanning depicts early malignant

bone-marrow infiltration because of the early increased glucose metabolism in neoplastic cells. FDG-PET scanning has limited spatial resolution, and complementary CT scanning or MRI is required to localize an area of increased glucose metabolism.

Isotopic imaging methods depict bone metastatic lesions as areas of increased tracer uptake. The classic pattern appears as the presence of multiple randomly distributed focal lesions throughout the skeleton Findings of a solitary scintigraphic abnormality or just a few lesions may present special problems in the interpretation of findings. Other patterns include diffuse involvement (superscan), photopenic lesions (cold lesions), normal scintiscans, flare phenomena, and soft-tissue lesions.

Sensitivities of Tc bone scintiscans are reportedly 62-89%. Many benign processes and normal variants can produce an area of increased isotope uptake that mimics a metastatic deposit. Solitary areas of abnormal uptake associated with benign processes occur in approximately one third of patients with malignant disease. The differential diagnosis of multiple scintigraphic abnormalities includes metabolic problems (Cushing's syndrome), osteomalacia, trauma, arthritis, osteomyelitis, Paget disease, and infarctions. Some metastases may produce normal scintiscan findings. Cold or photopenic metastases may be found in association with lesions of highly aggressive anaplastic carcinomas. In diffuse metastatic disease, isotopic accumulation may be sufficiently uniform to produce a false-negative impression. Clues to the detection of the so-called superscan include skeletal uptake of greater-than-normal intensity, in relation to the background of the soft tissue and the low or absent uptake in the kidneys.

Osteoblastic activity that reflects attempts at bone healing after chemotherapy (flare phenomenon) may misleadingly suggest advancing disease on scintigraphy. The number of false-positive scintiscans can be decreased if the findings are reviewed with the corresponding radiographs. In a comparative study of 3 modalities, Daldrup-Link et al found sensitivities of 90% for FDG-PET scanning, 82% for whole-body MRI, and 71% for 99m Tc bone scintiscans (11). FDG-PET scanning shows a high number of false-positive lesions, which require follow-up imaging with other modalities. The use of semiquantitative criteria for tumor FDG uptake in the qualitative evaluation of images may increase the specificity. In skull metastases, the high rate of glucose metabolism in the normal areas of brain may obscure metastases.

Given the ability of FDG-PET to identify metabolically active skeletal metastases, which may or may not have detectable structural destruction, its use as an initial staging study and during follow-up evaluation is increasing for several malignancies such as lung, breast, and head and neck cancers. Early detection of malignant bone marrow infiltration can be demonstrated by increased glucose metabolism. Although FDG-PET is superior in detecting osteolytic metastases, it is less sensitive than 99mTc bone scans for detection of osteoblastic metastases.18,19 Therefore, the sensitivity of FDG-PET may vary among different histologies. When compared with 99mTc bone scan, FDG-PET is more sensitive for myeloma, equivalently sensitive for breast and lung cancers, and less sensitive for prostate cancer. The aggressiveness of the tumor may also influence the sensitivity of detecting bone metastases using FDG-PET.20

Skeletal PET using F-18 sodium fluoride (NaF-18), a positron-emitting bone-seeking tracer, is another unique nuclear imaging modality. The available literature shows that NaF-18 PET is substantially more sensitive and specific than 99mTc bone scan and SPECT 21,22 for detection of metastases, especially for osteolytic lesions, but higher cost and greater radiation dose are among the disadvantages of NaF-18 PET.23 Further studies focusing on cost-effectiveness may optimize the use of bone PET. All nuclear imaging modalities have limited spatial resolution, and therefore complementary CT is needed for localization of regions with abnormal glucose metabolism.

CT and MRI can evaluate suspicious findings on 99mTc bone scans and can provide better spatial resolution and three dimensional anatomic information about the skeleton as well as soft-tissue involvement. CT is recommended to evaluate structural integrity since CT is superior to MRI in revealing cortical integrity and the extent of structural destruction. MRI is highly sensitive to detect small skeletal metastases not yet detectable on bone scans by revealing abnormal bone marrow; focal low-signal intensity on a T1-weighted image mix/high intensity on a fat-suppressed T1-weighted image and high intensity on a T2-weighted image are diagnostic of metastases. MRI is particularly useful in detecting vertebral metastases and in determining disease extension around the spinal cord,

aiding surgical and/or radiation therapy planning. A disadvantage of MRI is that it may be difficult to distinguish changes due to treatment, fracture, or tumor.

Diagnosis

Incidentally detected bone lesions must be proven histologically using image guided appropriately placed needle biopsies. It is important to remember that these patients could have other benign and malignant neoplasms of the bone. In patients with a known malignancy, if the patient has other sites of metastases that are histologically proven, and if the bone lesion looks malignant radiologically, a biopsy need not be performed. If however bone is the first site of metastasis or if does not appear malignant on radiology, a biopsy would be indicated.

Therapeutic options

While detection of metastatic bone disease will change the therapeutic objectives and possibly modify treatment, there is little evidence to suggest early treatment of such metastases improves survival of patients. The goals of treatment when faced with asymptomatic skeletal metastases are two fold: 1) control tumour locally and 2) prevent skeletal related events (SRE). Most asymptomatic bone metastases are small with minimal risk for fracture. As they grow in size with associated cortical destruction, they develop pain and the risk of fracture increases. These may be solitary or multiple. Asymptomatic hypercalcemia may be seen. Early detection and aggressive management of metastases can improve the quality of life and functional independence of patients. Often the treatment recommendation is tailored to each patient's clinical presentation.

Treatment of bone metastases depends on the performance status of the patient, co-morbid illnesses, sites of metastases, extent of disease, risk assessment for fracture or cord compression and expected survival period. Both osteolytic and osteoblastic lesions can result in pain and fracture. Best results are achieved when treatment decisions are made by an interdisciplinary team including radiologists, pathologists, radiation oncologists, medical oncologists, orthopaedic surgeons or neurosurgeons, pain medicine specialists, physiotherapists and palliative care professionals. Treatment of bone metastases will involve a combination of chemotherapy, surgery, external beam radiotherapy (EBRT), hormonal therapy (HT), osteoclast inhibitors (OI), and radiopharmaceuticals.

Under current practice, systemic chemotherapy and/or HT and osteoclast inhibition (12,13) are frequently administered when asymptomatic bone metastases are first diagnosed. EBRT is usually delayed until the metastatic disease progresses and causes significant pain or creates a risk for pathological fracture or spinal cord compression. The use of radiopharmaceuticals is generally considered in a small fraction of patients with persistent multifocal sites of pain or recurrence of pain in a previously irradiated site.

The optimal management of oligometastases is an active area of research(12,13). Investigations comparing site-specific localized therapy to a more systemic approach with or without localized therapy are ongoing. Patients with minimal sites of bone-only metastatic disease (deemed "oligometastatic") have a longer survival when compared to patients with multiple/ visceral metastases. It is possible that these have a different biology and some may be treated with curative intent, though evidence to this effect is not strong. Solitary lesions, especially after a long disease free interval may be resected with 'intent to cure'.

Systemic Therapy

Bisphosphonates (14) bind preferentially to bone at the site of active bone resorption and inhibit bone resorption by blocking recruitment and activation of osteoclasts. (Figure 6) Pamidronate and zoledronic acid are used to treat cancer-related bone complications. In several randomized clinical trials, intravenous bisphosphonate therapy was shown to delay the onset and lower the incidence of SREs in patients with bone metastases from solid tumors and multiple myeloma. The optimal duration of bisphosphonate therapy has yet to be determined, and therefore patients usually remain on this therapy indefinitely. Recognized effects of the toxicities of potent osteoclast inhibitors include renal dysfunction (with intravenous bisphosphonates), hypocalcemia, and osteonecrosis of the jaw. Dose modifications are made based on the creatinine clearance.

Denosumab (15), a human monoclonal antibody that binds and neutralizes receptor activator of nuclear factor κB ligand (RANKL), protects bone from degradation. Several recently published randomized clinical trials demonstrated that denosumab was superior to zoledronic acid in delaying the time to first SRE in patients with breast cancer and other solid tumors.

For certain malignancies that involve bone, such as myeloma and lymphoma, systemic chemotherapy may treat the bone lesions as well. In addition to radionuclide therapy, androgen deprivation therapy is another systemic treatment option for widespread bone metastasis from prostate cancer.

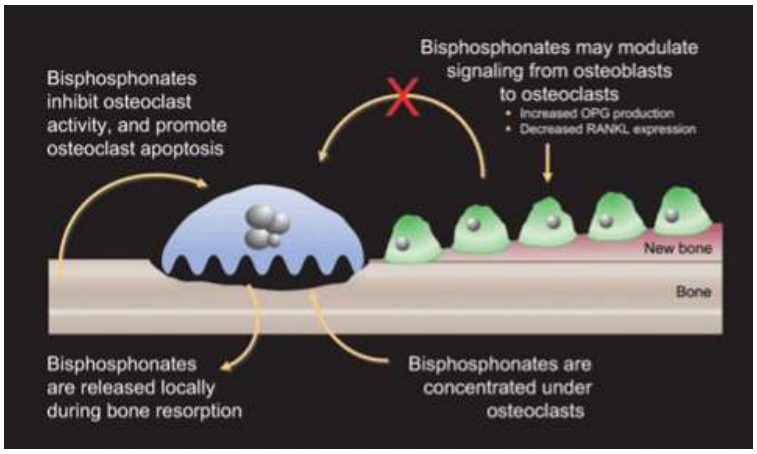


Figure 6
(From Ref.6)

Radiation therapy(16)

Radiotherapy is not commonly recommended for asymptomatic bone metastases that are not associated with a risk of pathologic fracture (low Mirel's score). Asymptomatic bone lesions that are at risk for but are not impending fractures can be treated with EBRT. This approach decreases the tumor burden and promotes regrowth of normal bone. EBRT may be delivered using telecobalt units or linear accelerators. Techniques of 3 dimensional conformal therapy (3 D CRT), intensity modulated radiation therapy (IMRT), image guided radiation therapy (IGRT) or stereotactic body radiation therapy (SBRT) may be used depending on the infrastructure and expertise available. Bisphosphonates and radiopharmaceuticals also play a role in the prevention of pathologic fracture. These modalities are complementary and are often used in combination. The acute side effects of palliative *external beam radiotherapy (EBRT)* are usually minimal and self-limiting, while long-term side effects are uncommon and often irrelevant in a patient group with limited life expectancy.

Surgery

Surgery is rarely necessary in asymptomatic bone metastases. Prophylactic fixation of impending pathological fracture may be considered for metastatic disease to the long bone if an osteolytic lesion involves more than 50% of the cortex circumferentially. Impending fractures are usually associated with pain. Percutaneous vertebral augmentation with polymethyl methacrylate can be used to optimize spinal stability. Both vertebroplasty and kyphoplasty improve mechanical stability of the vertebra and reduce pain in patients who have vertebral body compression fractures without neurologic deficits. Their role in asymptomatic vertebral metastases is unclear. Surgical resection may be considered for solitary bone metastasis after a long disease free interval. This may provide an opportunity for 'cure'.

Fracture risk assessment

There are criteria for determining the risk of pathologic fracture [Harrington's(16) and Mirels'(17)] and spinal instability in the setting of osseous metastasis. Harrington lists four criteria that increase the risk of pathologic fracture: destruction of the metaphysis (>50-75%) or diaphysis (>50% or 2.5 cm), destruction of the subtrochanteric femoral region and persistent pain following radiation therapy. Mirels' criteria assign a score to each of four factors: site, type and size of the lesion and the type of pain. A score of >8 suggests prophylactic fixation should be considered. The Spinal Instability Neoplastic Score (SINS) (18,19) also assigns a score for the location of the lesion, type of pain, spinal alignment, extent of vertebral body collapse and presence of involvement of the posterolateral spinal

elements. The composite score then places patients into groups of spinal stability. Patients with a score of 7 or greater should undergo evaluation for prophylactic stabilization.

The Mirels system (classifies the risk of pathologic fracture based on scoring four variables on a scale of 1-3: location of lesion, radiographic appearance, size, and pain. An overall score is calculated, and a recommendation for or against prophylactic fixation is made.

Table 1:

	1	2	3
Location	Upper extremity	Lower extremity	Intertrochanteric
Radiographic appearance	Blastic	Mixed	Lytic
Size[a]	< 1/3	1/3-2/3	>2/3
Pain	Mild	Moderate	Functional

[a]Size is determined as a fraction of the cortical thickness.
[b]Functional pain is defined as severe pain or pain aggravated by limb function.

Table 2:

Score	Fracture Risk	Recommendation
≥9	33%-100%	Prophylactic fixation is recommended
=8	15%	Clinical judgment should be used
≤7	<4%	Observation and radiation therapy can be used

An alternate system would be to use Harington's criteria**: Table 3**

- **> 50% destruction of diaphyseal cortices**
- > 50-75% destruction of metaphysis (> 2.5 cm)
- Permeative destruction of the subtrochanteric femoral region
- Persistent pain following irradiation

An evidence-based process using the best available literature and expert-opinion consensus was used to develop the Spine Instability Neoplastic Score (SINS)(18-19). In this classification system, tumor-related instability is assessed by adding together six individual component scores: spine location, pain, lesion bone quality, radio-graphic alignment, vertebral body collapse, and posterolateral involvement of the spinal elements. The minimum score is 0, and the maximum is 18. A score of 0 to 6 denotes stability, 7 to 12 denotes indeterminate (possibly impending) instability, and 13 to 18 denotes instability. A surgical consultation is recommended for patients with SINS scores greater than 7.

Surgical treatment algorithm

- Obtain tissue diagnosis
  - Biopsy all solitary bone only metastasis
  - If biopsy suggests primary neoplasm of bone treat appropriately

- Radiation therapy
  - Low Mirels' score

- Surgical fixation
  Goals of fixation
  - maximize ability for immediate mobilization and weight-bearing
  - protect the entire bone in setting of systemic or metastatic disease
  - optimize implant choice in the context of the patient's overall prognosis
  - type of fixation depends on location of lesion and type of disease

SINS Component	Score
Location	
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	3
Mobile spine (C3-C6, L2-L4)	2
Semirigid (T3-T10)	1
Rigid (S2-S5)	0
Pain*	
Yes	3
Occasional pain but not mechanical	1
Pain-free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
> 50% collapse	3
< 50% collapse	2
No collapse with > 50% body involved	1
None of the above	0
Posterolateral involvement of spinal elements†	
Bilateral	3
Unilateral	1
None of the above	0

Table 4

Abbreviation: SINS, Spinal InstabilityNeoplastic Score.
Pain improvement with recumbency and/or pain with movement/loading of spine
†Facet, pedicle, or costovertebral joint fracture or replacement with tumor.

Humerus

- proximal humerus lesions - endoprosthesis
- diaphysis
  - intramedullary nail
  - resection and intercalary spacer
  - plates and screws (less preferred)
- distal humerus lesions
  - flexible nails
  - elbow replacement

Femur

- peritrochanteric lesions - intramedullary nail
- femoral neck and head lesions - hemiarthroplasty

- Postoperative radiation
  All patients treated surgically must receive post-operative radiotherapy to
  - decrease pain
  - slow progression
  - treat remaining tumor burden not removed at surgery

Patients who undergo surgical stabilization for impending or completed pathologic fracture of a long bone may be treated with postoperative radiotherapy to 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions or 8 Gy in a single fraction.

Radiopharmaceuticals (21) have a limited role in the management of asymptomatic skeletal metastases. Multiple small painless metastases that are not likely to fracture would be a possible indication in addition to appropriate chemotherapy, hormonal and osteoclast inhibitor therapy.

For predominantly osteoblastic diffuse bone metastases, radionuclide therapy has the advantage of treating multiple sites simultaneously. The currently available radiopharmaceuticals deliver a

therapeutic dose of beta radiation and include strontium-89, samarium-153, and phosphorus-32. These radionuclides concentrate in actively calcifying areas by binding to hydroxyapatite, with a high affinity in metastatic sites, where there is rapid bone turnover. Inhibition of lymphocyte-associated cytokines or alterations in osteoclast or osteoblast activity are thought to be the underlying mechanism for pain relief. An alpha-emitting radioisotope is another category of radionuclide therapy. It has promising efficacy with minimal myelotoxicity. The side effects of radiopharmaceuticals include bone marrow suppression, which is usually temporary and may be worse in heavily pretreated patients.

To objectively assess and quantify quality of life in patients with bone metastases, several questionnaire-based tools have been developed. For example, the European Organisation for Research and Treatment of Cancer recently developed the Quality of Life Questionnaire (EORTC QLQ-BM22), a 22-item module designed to measure symptoms, functions, treatment side effects, psychosocial variables, and expectations of patients with bone metastases. Tools such as these can improve the ability to evaluate baseline measures and outcomes after a chosen therapeutic regimen for bone metastases and allow physicians to recommend certain interventions tailored to the needs of each individual patient.23.

Take home message

- Breast, prostate and lung primaries are the commonest source of bone metastases.
- Normal bone is constantly being re-modeled through a cycle of new bone formation and resorbtion mediated by osteoblasts and osteoclasts.
- Receptor activator of nuclear factor kappa B (RANK) expressed on the surface of the osteoclast is a key factor in control of osteoclast activity.
- The nature of the bone metastases -osteoblastic or osteolytic or mixed depends on the type of malignancy.
- Osteolytic lesions occur when tumour cells secrete osteoclast activating factors- IL-6, IL-8, and IL-11, tumour necrosis factor (TNF), macrophage colony-stimulating factor (M CSF), prostaglandin E2, and PTH-RP. The bone matrix in turn secretes tumour growth factors like transforming growth factor beta (TGF-beta), insulin-like growth factors, fibroblast growth factors, platelet-derived growth factor, and bone morphogenetic proteins. The osteoclast activity is more than the osteoblasts capacity to lay down new bone.
- In addition myeloma cells secrete inhibitors of osteoblasts resulting in purely lytic lesions.
- Sclerotic bone metastases occur when the tumour secretes osteoblast activating factors like endothelin, fibroblast growth factors and bone morphogenic proteins. In addition malignant cells also activate osteoclasts which in turn promotes more malignant cell activity.
- Patients with bone metastases may also have visceral metastases.
- Solitary bone only lesions in patients with a known malignancy could also be a primary bone neoplasm. They must be biopsied.
- Survival of patients with bone metastases ranges from a few months (lung) to a few years (prostate and breast).
- Patients with bone only metastases tend to have a longer survival than those who also harbour visceral metastases.
- Patients with oligometastases should be treated aggressively with 'intent to cure'.
- Tc99m bone scan is the investigation of choice to screen for bone metastases. Aggressive bone metastases with excess of osteolytic activity might be missed on bone scans.
- PRT scans (FDG or F18) can be more sensitive than Tc 99m bone scans. They have excellent negative predictive value. In addition they also help screen other organs for metastases.
- All asymptomatic bone metastases are usually small with a low risk of complications. They do have the potential to grow and result in pain and other skeletal events.
- Asymptomatic skeletal metastases with low risk for fracture are treated with bisphosphonates or RANK inhibitors.
- Radiation therapy may be considered when the risk of fracture is assessed to be significant.
- Fracture risk in long bones is assessed using the Mirels' or Harington's criteria.
- Risk of vertebral/ spinal complications is assessed using the Spinal Instability Neoplastic Score.
- Surgery is rarely indicated for asymptomatic bone metastases. Solitary bone metastasis after a long disease free interval could be considered for resection with intent to cure.

- Quality of Life issues are of utmost importance when dealing with patients with metastatic disease.
- Management algorithms: Figures 7 & 8 from reference 1

Figure 7

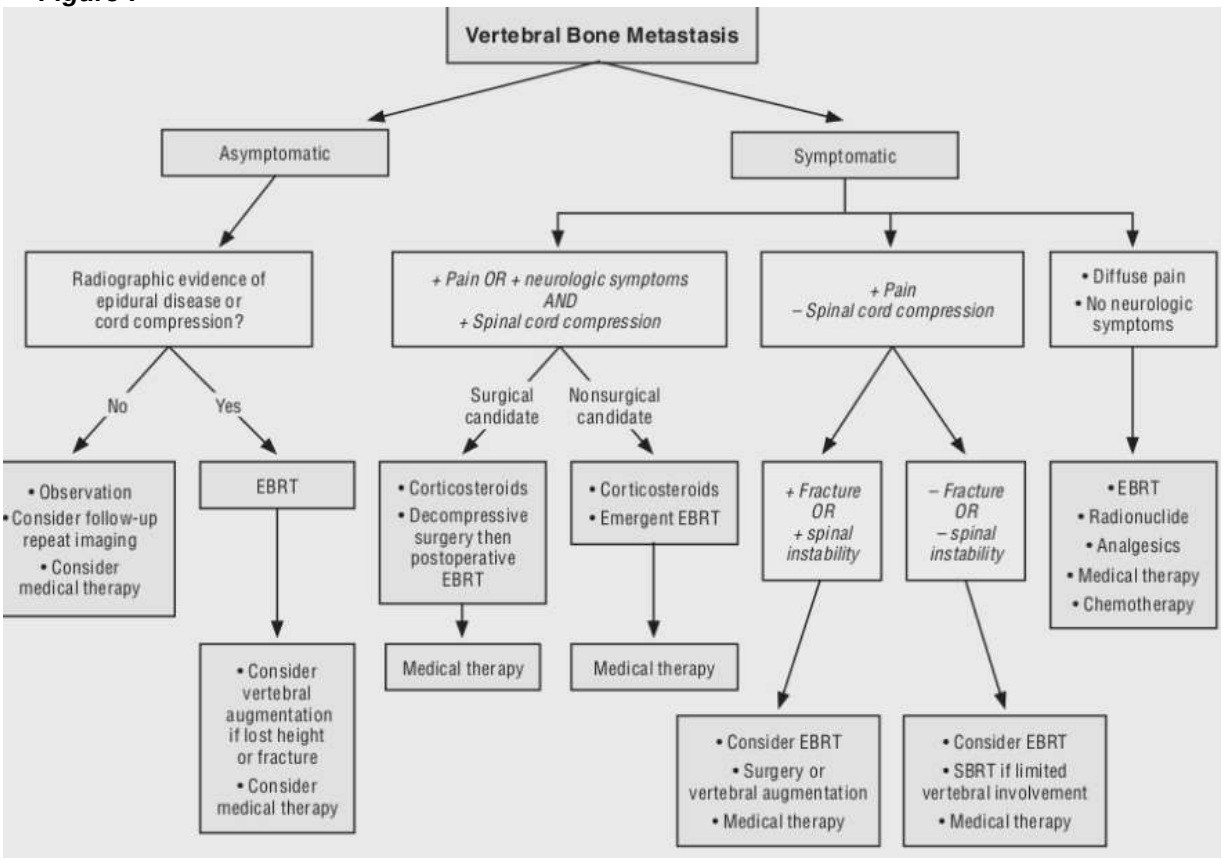
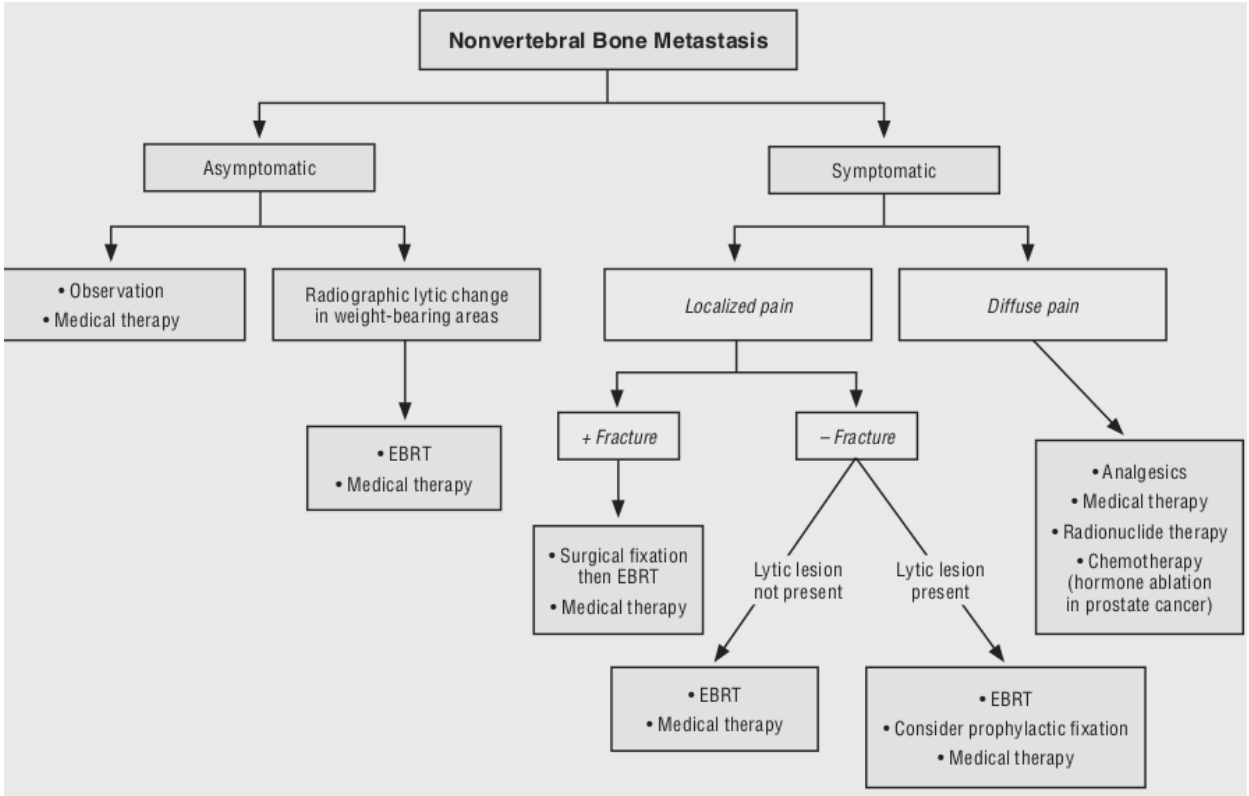


Figure 8



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Graves opthalmopathy

A.K.Sarda, Pawan Lal

The causes of graves opthalmopathy are enlargement of the extra-ocular muscles and retroocular connective tissue behind the globe. This displaces the globe anteriorly to cause proptosis. The enlarged and fibrotic muscles do not relax and restrict the motions of the eye ball resulting in diplopia. Lid retraction occurs due to spasm of Muller's muscle. Proptosis combined with lid retraction may lead to exposure keratitis. The enlarged muscles at the apex of the orbit may compress the optic nerve causing optic neuropathy. Chemosis and peri-orbital edema results from local inflammation and impaired orbital venous drainage.

The eye involvement in Graves disease is auto-immune response.

Ophthalmopathy	
Incidence	
Eyelid signs excluded	10 – 25 %
Eyelid signs included	30 – 40 %
Severe opthalmopathy	5%

Opthalmopathy is bimodal with peak incidence in the age groups 40 – 44 years and 60 – 64 years. Severe opthalmopathy is more common in men and higher prevalence is seen in cigarette smokers.

Noninfiltrative Ophthalmopathy

Almost all patients with active thyrotoxicosis have some abnormality that is detectable on careful examination of their eyes. This abnormality may be only widening of the palpebral fissure, lag of the globe on upward gaze, or lag of the upper lid on downward gaze, producing an increase in the visible segment of the sclerae and a bright-eyed or pop-eyed appearance. These abnormalities cause the eyes to appear exophthalmic, but measurement may show that there is no proptosis. Similar changes may be produced by administration of thyroid hormone or by local action of sympathetic stimuli on Müller's superior palpebral muscle, causing spasm and retraction of the upper lid. This variety of ophthalmopathy is valuable diagnostically, and although it may have some undesirable cosmetic effect, it carries no hazard to ocular function. These findings are corrected by control of the thyrotoxicosis, no matter which therapeutic route is followed. It should be noted in passing that lid lag is fairly common in normal subjects.

Infiltrative Ophthalmopathy

Infiltrative ophthalmopathy is considered a characteristic and unique feature of Graves' disease. It may coexist with the noninfiltrative ophthalmopathy described above, but it is a separate disorder.

Etiology

The thyroid gland itself does not cause thyroid-associated orbitopathy (TAO), and regulation of thyroid function does not abort this condition. Rather, the thyroid gland, eye muscles, and pretibial skin are especially subject to the autoimmune attack. However, restoration of the euthyroid state (with antithyroid drugs and thyroxine) may improve the eye status to some extent.

Thyroid state and irradiation

Many patients with thyroid-associated orbitopathy are hyperthyroid, but euthyroidism (20%), Hashimoto thyroiditis, thyroid carcinoma, and neck irradiation are also associated with thyroid-associated orbitopathy. Even if the patient is euthyroid, thyroid-associated orbitopathy may progress. In patients who are hyperthyroid, the eye signs of thyroid-associated orbitopathy usually develop within 18 months of dysthyroidism; very often, they develop concurrently.

Radioactive iodine

Although somewhat controversial, several publications have suggested that thyroid ablation with orally ingested radioactive iodine-131 (RAI) (^{131}I) may exacerbate thyroid-associated orbitopathy compared with antithyroid drugs or surgical ablation. However, several studies have not shown that radioiodine is a significant risk for initiation or progression of mild thyroid-associated orbitopathy.[7, 8] ^{131} I is believed to cause a release of thyroid antigens. In a study by Bartalena, approximately 15% of patients treated with only radioactive iodine developed or had worsening of thyroid-associated orbitopathy.[9] However, some authors feel the threshold for diagnosis of thyroid-associated orbitopathy was low (eg, ocular irritation). In contrast, none of the patients treated with both radioactive iodine and prednisone had progression of thyroid-associated orbitopathy, and two thirds showed improvement.[9] Only 3% of patients treated with methimazole showed worsening of thyroid-associated orbitopathy.

Diseases associated with thyroid-associated orbitopathy

Autoimmune diseases such as myasthenia gravis, Addison disease, vitiligo, and pernicious anemia have been described with thyroid-associated orbitopathy. In one study, 8% of patients with this condition had positive acetylcholine receptor antibodies[10]; however, at 4.5-year follow-up visits, none of the patients with positive serology was identified clinically to have myasthenia gravis. *Yersinia enterocolitica* infection has been also associated with thyroid-associated orbitopathy.

Smoking
Thyroid-associated orbitopathy is associated strongly with smoking[11, 12] ; the more severe the eye disease, the stronger the association. In one study, smokers of European ethnicity had a 2.4 times increased risk for this condition compared with their Asian counterparts. Active smokers require more strabismus surgery than nonsmokers, independent of orbital decompression surgery.[13]

Pathology
TED involves histologic abnormalities in orbital tissues including extraocular muscles, orbital fat, lacrimal glands and interstitial connective tissue. On gross inspection extraocular muscles are enlarged, firm and have a rubbery consistency. Microscopically intense infiltration is seen by mononuclear inflammatory cells like lymphocytes, plasma cells, macrophages and mast cells. Interstitial edema is almost invariably present. The muscle fibers may be normal using light and electron microscopy as well. In end stage ophthalmopathy fibrosis and infiltration of extraocular muscles is present. Affection of extraocular muscles is in most instances asymmetrical. The medial and inferior recti are more frequently involved than the superior or lateral recti or the oblique muscles. Lacrimal glands often show mild mononuclear infiltration and interstitial edema. Fibrosis however does not occur.

Pathophysiology
In simplest terms, the underlying pathophysiology of thyroid-associated orbitopathy is thought to be an antibody-mediated reaction against the thyroid-stimulating hormone (TSH) receptor with orbital fibroblast modulation of T-cell lymphocytes. T-cell lymphocytes are believed to react against thyroid follicular cells with shared antigenic epitopes in the retroorbital space. An active phase of inflammation is initially present.

Lymphocytic infiltration, fibroblast reaction, and increased orbital volume
Lymphocytic infiltration of the orbital tissue causes a release of cytokines (eg, tumor necrosis factor [TNF], interleukin 1 [IL-1]) from CD4+ T cells stimulating the orbital fibroblasts to produce mucopolysaccharides, which, by hyperosmotic shift, cause tissue edema in the extraocular muscles.

Fibroblasts are believed to be the target and effector cells in thyroid-associated orbitopathy. Fibroblasts are extremely sensitive to stimulation by cytokines and other soluble proteins and immunoglobulins that are released in the course of an immune reaction. The cytokines activate previously quiescent fibroblasts to secrete hyaluronic acid, a glycosaminoglycan. Doubling the hyaluronic acid content in the orbital tissue causes a 5-fold increase in the tissue osmotic load. In addition, preadipocyte fibroblasts are influenced to transform into adipocytes, especially in young patients.

The orbit can be described as a pear-shaped box with an anterior opening; the stalk of the pear represents the optic nerve. In thyroid-associated orbitopathy, the increase in orbital volume from the extraocular muscles and fat causes forward protrusion (proptosis or exophthalmos) and, occasionally, optic nerve compression at the narrow posterior apex of the orbit. The edema results in tissue damage and fibrosis, with restriction in extraocular motility and lagophthalmos.

Usually within 1-2 years of the onset of orbital involvement, the inflammation settles to a more quiescent, fibrotic phase predominated by scarring of the orbital tissues.

Potential pathoimmunology
Thyroid-associated orbitopathy may be part of a more generalized disorder of connective tissue and striated muscle.[14] A more extensive discussion on the pathoimmunology of thyroid-associated orbitopathy is beyond the scope of this article. However, some of the research in this field is outlined below.

The insulinlike growth factor 1 receptor (IGF-1R) is an autoantigen that may be important in thyroid-associated orbitopathy, because of its aberrant expression by thyroid-associated orbitopathy fibroblasts, the promotion of T-cell recruitment, and the presence of circulating activating autoantibodies. T helper 2 cytokines (IL-4 and IL-13) may induce the expression of 15-lipoxygenase-1, with upregulation in the production of 15-hydroxyeicosatetraenoic acid (15-HETE), causing tissue activation and remodeling.

Cyclooxygenase 2 (COX-2) is expressed at higher levels in the orbital fibroadipose tissues of thyroid-associated orbitopathy. There is a positive correlation with increasing severity of orbital disease,

suggesting a possible relationship with COX-2 expression and orbital inflammation in thyroid-associated orbitopathy.

Variants in the *IL-23R* gene are strongly associated with Graves ophthalmopathy (or thyroid-associated orbitopathy). These variants may predispose to this condition by changing the expression and/or the function of *IL-23R*, thereby promoting a proinflammatory signaling cascade.

The role of clathrin-mediated signalling pathways,[15] palmitate,[16] and Thy-1 surface markers[17] on orbital fibroblasts as they relate to the pathogenesis of TAO remains to be seen.

Incidence and Course

In 75% of patients ophthalmopathy manifested itself between one year before or one year after appearance of hyperthyroidism. Ophthalmopathy however, may appear long before manifestation of thyrotoxicosis or even decades after hyperthyroidism has been successfully treated. In fact, it may occur in patients who never develop clinical hyperthyroidism. The disease may be unilateral or bilateral, may begin in one eye, or may always be more severe in one eye than in the other. Usually the syndrome accompanies hyperthyroidism and is at its worst when the diagnosis is first made. No more than 2 - 5% of patients with Graves' disease develop progressive severe exophthalmos. This progression often happens without a clear correlation with the severity of stage of the thyrotoxicosis. In some of these patients, the process continues inexorably to complete blindness unless heroic therapeutic measures are taken, and sometimes despite these efforts. Although thyrotoxicosis occurs in women about five times more frequently than in men, progressive ophthalmopathy occurs relatively more frequently and is relatively more severe in men and increases with age.It is rare in children.

Since exophthalmos usually improves with treatment of thyrotoxicosis, the patient should be restored to the euthyroid state as soon as possible and kept there. In treating the hyperthyroidism of these patients, it is important that they not be allowed to become hypothyroid later. Hypothyroidism seems to accentuate the signs and symptoms of the ophthalmopathy, possibly by increasing the water content of the tissues.

SIGNS AND SYMPTOMS

The signs and symptoms are produced by the following related abnormalities .

- ***Edema of the orbital contents***. The lids and periorbital tissues are irritated, injected, and characteristically swollen and puffy. The lids may be erythematous. The swollen lids usually feel firm and do not pit. There is chemosis, and edema of the scleral conjunctiva. Edematous conjunctiva may even protrude beyond the palpebral fissure. Associated with this condition may be excessive lacrimation and photophobia. The lacrimal gland may be almost totally destroyed by the infiltrative lesion. Nevertheless epiphora is typical. Eye pain, irritation, and "grittiness" of the eyes are common complaints.

- ***Protrusion of the globe***. It is unusual for the anterior border of the cornea to protrude normally more than 18 mm beyond the lateral margin of the orbit. If measurements with the Leudde or Hertel exophthalmometer show that the globe is 2 or 3 mm beyond this limit, then true proptosis is present (normal limits may be race-dependent). Often the globes cannot be easily displaced backward by digital pressure. When this displacement is attempted, the examiner senses that the retrobulbar tissue is firm and unyielding. Associated with this condition, and responsible for exophthalmos, is an increase in the volume of orbital contents including fatty tissue and muscles. The lacrimal gland may be enlarged and palpable, and even visible. Prolapse of the globe beyond the orbital fissure in extreme proptosis may permit a startling closure of the lids behind the globe.

  The patient or friends usually note these abnormalities as an increased prominence of the eyes or a "staring" or "wild" expression. Occasionally there is a severe pain behind the eyes. Exophthalmos causes the exposed conjunctivae to be more readily irritated by all noxious agents. If the lids fail to close completely over the cornea while the patient sleeps, development of ulceration is a hazard.

- ***Infiltration of the extraocular muscles.*** The muscles become infiltrated, inflamed, and enlarged. Inflammation of the muscles gives rise to an important and characteristic sign that we find helpful in differentiating the ophthalmopathy of Graves' disease from other causes of

exophthalmos. The insertion of the swollen lateral rectus is often visible as a beefy red area at the inner and outer canthus when the patient turns the eye laterally or medially. Normally the muscle insertion is barely visible and is pale pink. In tumors or other retrobulbar lesions, this change in muscle insertion is not seen. The enlargement is almost pathognomonic of Graves' disease.

Paralysis, or paresis, of the extraocular muscles occurs. Upward gaze is affected first and most seriously, and loss of convergence is common. Oculomotor paralysis may be severe when exopthalmos is minimal or absent, but the changes are usually more or less parallel. These changes in ocular muscle function often initially produce diplopia. As the lesion progresses, a permanent strabismus may develop, with coincident suppression of the visual image in one eye and loss of the diplopia. Oculomotor function is occasionally lost completely.

The initial inflammatory lesion is followed gradually by recovery and fibrosis, and often the scarred and fibrotic muscle causes a fixed strabismus that persists indefinitely unless corrected surgically.

The oculomotor paresis is occasionally seen without significant exophthalmos or edema, and may be difficult to distinguish from myasthenia gravis or from paresis that is part of the neuropathy of diabetes. In such cases, it is wise to test for the presence of myasthenia by injection of 2-10 mg edrophonium intravenously. The function of muscles damaged by the ophthalmopathy of Graves' disease is not significantly improved during the test. Myasthenic weakness will be corrected within 1 minute and the benefit will last for several minutes, depending on the dose.

- ***Damage to the optic nerve and the retina.*** The retina may be injured by venous congestion or hemorrhages. Field defects are occasionally found. Papilledema may be present, especially in severe involvement of the eye. If the optic nerve is involved, there may be pallor of the optic disc and a decrease in central visual acuity or field cuts, valuable and ominous signs. Blindness may occur without protrusion of the globe. Thus, TED may have the clinical features of optic neuritis.

  The clinical picture is altered by subsequent complications. The edematous conjunctivae are easily irritated by wind, smoke, or dust, and frequently become infected. Panophthalmitis is a most feared complication. Corneal ulcers are a serious hazard and may not heal while exophthalmos persists.

TAO Classification

Numerous classification systems for thyroid-associated orbitopathy (TAO) exist, but they all have shortcomings.

Types I and II

The simplest classification for thyroid-associated orbitopathy is type I and type II; these 2 types are not mutually exclusive. Type I is characterized by minimal inflammation and restrictive myopathy. Type II is characterized by significant orbital inflammation and restrictive myopathy.

NOSPECS

The Werner NOSPECS classification system (and its modifications) is one of the most commonly known systems and is used in many endocrine studies. NOSPECS uses a mnemonic to describe the presence or absence of signs or symptoms (NO) and grade and classify the severity and rank order of various clinical features (SPECS) (*s* oft-tissue involvement, *p* roptosis, *e* xtraocular muscle involvement, *c* orneal involvement, and *s* ight loss). Unfortunately, the NOSPECS classification has some weaknesses that may limit its prognostic value. Patients may fall into more than 1 particular class, and they may not progress in an orderly fashion from class 1 to class 6. In addition, patients with visual loss from compressive optic neuropathy may not show marked proptosis or other signs of severe disease.

Assessment of disease activity and severity

The natural history of the disease is one of rapid deterioration followed by gradual improvement toward the baseline. This active phase is best described by the Clinical Activity Score (CAS). The

CAS is generated by the addition of one point for each of the following features if present: pain in primary gaze, pain with eye movement, chemosis, eyelid swelling, eyelid erythema, conjunctival redness, caruncula swelling, and, over the prior 3 months, decreased visual acuity, increased diplopia, and proptosis (Table 1). The score ranges from 0 to 10 and predicts response to anti-inflammatory therapies. A 7-point scale, lacking the last three elements, is used when no previous assessment is available. GO is considered active in patients with a CAS ≥ 3. Therefore, hyperthyroid patients having only lid retraction alone, or in conjunction with mild conjunctival erythema and eyelid swelling, are not considered to have active GO.

Table 1: Assessmentof Graves' Ophthalmopathy: Clinical Activity Score Elements

Elements[a]	*Each visit*	*Comparison with previous visit*	*Score*
Painful feeling behind the globe over last 4 weeks	X		1
Pain with eye movement during last 4 weeks	X		1
Redness of the eyelids	X		1
Redness of the conjunctiva	X		1
Swelling of the eyelids	X		1
Chemosis (edema of the conjunctiva)	X		1
Swollen caruncle (fleshy body at medial angle of eye)	X		1
Increase in proptosis ≥2 mm		X	1
Decreased eye movements ≥5− any direction		X	1
Decreased visual acuity ≥1 line on Snellen chart		X	1

Adapted from Mourits et al., 1989 (310); and Mourits et al., 1997 (311).
[a]A 7-point scale (excluding the last three elements) is used when no previous assessment is available. GO is considered active in patients with a CAS ≥3.

The severity of the disease is best assessed using objective, quantifiable parameters and is a useful tool for directing therapy. The main gradations of disease severity are mild, moderate to severe, and sight threatening. Table 2 lists the elements as agreed upon in a consensus statement by the European Group on Graves' Orbitopathy (EUGOGO). Both activity and severity of the disease must be considered in therapeutic decisions regarding treatment of the eye disease itself, as well as treatment of hyperthyroidism. The overall evaluation and management of GO is best done in a multidisciplinary clinic combining endocrinologists and ophthalmologists with expertise in the condition and other specialties in consultation (e.g., ENT, radiation therapy, plastic surgery, and endocrine surgery).

Table 2: Graves' Ophthalmopathy Severity Assessment

Grade[a]	*Lid retraction*	*Soft tissues*	*Proptosis*[b]	*Diplopia*	*Corneal exposure*	*Optic nerve status*
Mild	<2 mm	Mild involvement	<3 mm	Transient or absent	Absent	Normal
Moderate	≥2 mm	Moderate involvement	≥3 mm	Inconstant	Mild	Normal
Severe	≥2 mm	Severe involvement	≥3 mm	Constant	Mild	Normal
Sight threatening	—	—	—	—	Severe	Compression

Adapted from de Juan et al., 1980 (313); Sarinnapakorn et al., 2007 (314); Tsai et al., 2006 (315); and Bartalena et al., 2008
[a]**Mild GO**: patients whose features of GO have only a minor impact on daily life, generally insufficient to justify immunosuppressive or surgical treatment. **Moderate-to-severe GO**: patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). **Sight-threatening GO**: patients with dysthyroid optic neuropathy and/or corneal breakdown. This category warrants immediate intervention.
[b]Proptosis refers to the variation compared to the upper limit of normal for each race/sex or the patient's baseline, if available.

Thyroid Disease Studies

Serum TSH (thyrotropin) is useful to establish a diagnosis of hyperthyroidism or hypothyroidism. Usually, the TSH is low in hyperthyroidism and high in hypothyroidism. Assays that measure the binding of TSH to a solubilized receptor are often referred to as TRAb (thyroid receptor antibody), TBII (TSH-binding inhibitor immunoglobulin), and LATS (long-acting thyroid stimulator) assays. Assays that measure the ability of immunoglobulin G (IgG) to bind to the TSH receptor on cells and to stimulate adenylate cyclase production have generally been referred to as the TSI (thyroid-stimulating immunoglobulin) assays. TSIs may show more significant association with the clinical features of TAO

than TBII and may be regarded as functional biomarkers for TAO.[19] Thyroid peroxidase antibodies and antibodies to thyroglobulin may be useful when trying to associate eye findings with a thyroid abnormality, such as euthyroid Graves disease.

CT Scanning and MRI

If the diagnosis of thyroid-associated orbitopathy (TAO) can be established clinically, then it is not necessary to routinely order a computed tomography (CT) scan or a magnetic resonance image (MRI). However, if these studies are required, obtain axial and coronal views.[20] MRI is more sensitive for showing optic nerve compression, whereas CT scanning is performed before bony decompression, because it shows better bony architecture.

Neuroimaging usually reveals thick muscles with tendon sparing. The inferior rectus muscle and the medial rectus muscle are usually involved. Bilateral muscle enlargement is the norm; unilateral cases usually represent asymmetric involvement rather than normality of the less involved side.

Isolated rectus muscle involvement may occur in up to 6% of patients; in this subgroup of patients, the superior rectus muscle may be the most frequently involved muscle. Isolated lateral rectus muscle enlargement without other evidence of muscle enlargement is uncommon in thyroid-associated orbitopathy and suggests another disease process (eg, orbital myositis).

Neuroimaging may also show a dilated superior ophthalmic vein. In addition, apical crowding of the optic nerve is well visualized (see the image below). Occasionally, the proptosis of thyroid-associated orbitopathy results in straightening of the optic nerve.
Axial computed tomography (CT) scan in a patient with congestive thyroid orbitopathy. The recti muscles are thickened with apical compression. The tendons are spared.
On CT scans, orbital fat density is higher in TAO patients, and it is negatively correlated to fat volume but positively correlated to muscle volume and muscle density.[21]

Therapy

Therapeutic possibilities include local measures to combat inflammation, glucocorticoids, plasmapheresis and immune suppressants, orbital radiation, decompressive surgery, and thyroid ablation. There is no perfect basis for selecting one form of therapy for coincident thyrotoxicosis over another, insofar as effects on the exophthalmos are concerned. Many thyroidologists believe that as long as eye signs are active, conservative treatment of the concomitant hyperthyroidism, i.e. medical treatment, is best to avoid worsening of TED even promote improvement. In this situation serum TSH is kept suppressed and FT4 in the high normal range in the assumption to keep antigen (TSH-R) release from the thyroid at a minimum.

Radioactive iodine as a treatment for the concomitant hyperthyroidism is considered by some authors as having a worsening effect on TED. Worsening could be prevented by temporary administration of prednisone. Several studies have been published concerning possible effects on development of eyesigns after partial thyroidectomy. The most recently published data indicate that ^{131}I therapy is more apt to be followed by worsening of exophthalmos than is surgical treatment. This may occur because of the well-recognized flair of autoimmunity produced by ^{131}.

Outpatient Management

- Most patients with thyroid-associated orbitopathy (TAO) can be observed; the follow-up interval depends on disease activity.
- Monitor for visual loss from corneal exposure and optic neuropathy and for strabismus development. The author does not recommend the use of eye exercises for patients with severe restrictive strabismus; doing so may elevate intraocular pressure.
- Visual field and color vision testing may help in early detection of visual loss.
- In patients with diplopia, prisms may be beneficial to those with small-angle and relatively comitant deviations.
- If a patient has dry eye symptoms, consider having them use artificial tears during the day, lubricating ointment at night, and punctal plugs. Tape occlusion of one lens or segment of the glasses may be helpful. If this does not work, try an occluder or vaulted eye patch (with care not to touch the cornea or compress the orbit).

Patient education

- Inform patients that thyroid-associated orbitopathy usually runs a self-limited but prolonged course over 1 or more years. Patients should also realize that no immediate cure is

available.[22] In addition, encourage patients to stop smoking to decrease the risk of congestive orbitopathy.

- Sleeping with the head of the bed elevated may decrease morning lid edema.

Steroids

Systemic steroids are usually reserved for patients with severe inflammation or compressive optic neuropathy in thyroid-associated orbitopathy (TAO). The consensus statement of the European Group on Graves' orbitopathy (EUGOGO) suggests intravenous glucocorticoids for patients with advanced thyroid-associated orbitopathy.[3] No cases of liver failure were seen in patients receiving less than 8 g of methylprednisolone.

Steroids may decrease the production of mucopolysaccharides by the fibroblasts. Pulse intravenous steroids (eg, methylprednisolone 1 g every other day for 3-6 cycles) can be considered but may only marginally improve long-term disease outcome. Thus, if necessary, high-dose steroids and higher intravenous doses are given for compressive optic neuropathy. If no response occurs after 48 hours, steroids probably will not work; at this point, the patient should have surgical decompression and maintain steroids.

Adjunctive cyclosporine, octreotide, and intravenous immunoglobulin (IVIg) are less common modalities of medical treatment for optic nerve compression. If a good steroid response occurs, orbital radiation may be considered. In severe cases of thyroid-associated orbitopathy, combined steroids, radiation, and surgery may be required. In patients with worsening TAO despite orbital decompression, intranasal steroids can be used.

Orbital Radiation

Orbital irradiation is sometimes is prescribed for moderate to severe inflammatory symptoms, diplopia, and visual loss in patients with thyroid-associated orbitopathy (TAO). The radiation (1500-2000 cGy fractionated over 10 d) is usually administered via lateral fields with posterior angulation. Radiation is believed to damage orbital fibroblasts or perhaps lymphocytes.

The radiation requires several weeks to take effect, and it may transiently cause increased inflammation. Thus, most patients are maintained on steroids during the first few weeks of treatment. In addition, better response to radiation is observed in patients with active inflammation who are treated within 7 months of the onset of thyroid-associated orbitopathy. Radiation may be more effective if combined with steroid treatment.

Studies that suggest that radiotherapy is ineffective in thyroid-associated orbitopathy must be scrutinized to ensure that the radiation was administered to appropriate candidates at the appropriate time. For example, the Gorman et al study used serum thyroid-stimulating immunoglobulin [TSI] as a surrogate of active eye disease.[27] Although the blood test is an indicator of immunologic activity, it may not reflect the clinical progression of thyroid-associated orbitopathy. Furthermore, the patients in that study were enrolled at a median of 1.3 y after the onset of eye symptoms, suggesting that many of the patients in the study would not have progressive eye symptoms or signs indicative of an ongoing orbital process.[27]

Although improvement of motility disturbances can occur with radiotherapy, radiation is limited when used in isolation to treat diplopia.

Potential adverse effects and contraindications

Cataract, radiation retinopathy, and radiation optic neuropathy are possible risks. These effects are not common if treatment is appropriately fractionated and the eyes are shielded. Marquez et al found 12% of their study patients developed cataracts after irradiation (median follow-up, 11 y).[28]

Wakelkamp et al also believed that orbital irradiation for thyroid-associated orbitopathy is a safe treatment modality, except possibly for patients with diabetes mellitus.[29] Radiation may be a relative contraindication for patients with diabetes mellitus because of the risk of worsening retinopathy.

Prevention of I-131-Associated TAO

To prevent progression of thyroid-associated orbitopathy (TAO) from radioactive iodine, pretreating and post treating the patient with low-dose steroids (eg, 0.5 mg/kg/d up to 2 mo posttreatment) has

been suggested if no contraindications for steroids exist and this therapy is agreed to by the patient. Following radioactive iodine, the patient should be monitored closely for the development of hypothyroidism.

Overview of Surgical Intervention

Approximately 5% of patients with thyroid-associated orbitopathy (TAO) may require surgical intervention. The patient should know that multiple-staged procedures may be required.[30, 31, 32] In elective cases, listen carefully to what the patient desires; the patient's expectations may not be realistic.

The timing of surgery is important. Unless compressive optic neuropathy or severe corneal exposure is present, surgery is generally delayed during the active inflammatory phase of thyroid-associated orbitopathy. Surgery is usually performed during the quiescent cicatricial phase of the disease.
Taking preoperative photographs is advised. With strabismus surgery, document prism measurements or fields of single binocular vision. Recording baseline-automated perimetry also is useful.

The sequence of surgery is also important. If the patient has marked proptosis, strabismus, and lid deformity, perform surgery in the following order:

1. Orbital decompression
2. Strabismus surgery
3. Lid-lengthening surgery
4. Blepharoplasty

These procedures will be briefly reviewed in the following sections.

Orbital Decompression

Orbital decompression may be performed as the initial treatment of compressive optic neuropathy or used if medical treatment is ineffective. A combination of medical and surgical treatment may be required in compressive optic neuropathy.

Thoroughly explain the potential complications of orbital decompression (eg, blindness, hemorrhage, diplopia, periorbital numbness, globe malposition, sinusitis, lid malposition) to the patient before surgery.

Procedure overview

Consists of producing increased space by herniating orbital contents into the adjacent ethomoid, maxillary sinuses or temporalis fossa. In case of thyroid orbitopathy with optic neuropathy, is it important to achieve adequate decompression at the apex of the orbit.Decompression of orbit is recommended only when the proptosis is more than 23mm – 24 mm. There are different approaches including anterior ethmoidal (Sewall), transantral (Orgura), lateral (Kronlein), transfrontal (Naffziger) and maxillary (Hirsch).An alternate route for maxillary and ethomoidal decompression is a transantral or Caldwell-Luc approach from below.

Orbital fat decompression

Orbital fat decompression without bony removal has been described for thyroid-associated orbitopathy (TAO) without apical compression. Candidates for orbital fat decompression should show predominant enlargement of the orbital fat compartment, rather than the rectus muscles on orbital imaging.

Unlike cosmetic blepharoplasty, with orbital fat decompression, fat is also removed posterior to the equator of the globe. Inferiorly, the fat is removed through a transconjunctival approach, which may be facilitated with lateral canthotomy and cantholysis. Superiorly, fat removal is through a lid crease incision, usually confined to the nasal quadrant.

A study by Liao et al confirms that a reasonable and effective reduction in proptosis can be safely achieved by extensive orbital fat removal alone.[33] The study did not correlate individual case results with extent of extraocular muscle hypertrophy compared with degree of fat hypertrophy, thus greatly impacting results in individual cases. The risk of postoperative worsened strabismus was not addressed and likely still remains a (theoretical) risk. Relying solely on fat decompression in cases of impending or actual optic nerve compression is not advisable.

Strabismus Surgery
Successful, early strabismus surgery during active thyroid ophthalmopathy has been described, but strabismus surgery generally is delayed until thyroid-associated orbitopathy (TAO) is inactive and the prism measurements have been stable for at least 6 months.

Patients should realize that the goal of surgery is to minimize diplopia in primary and reading positions. Expecting binocular single vision in all positions of gaze may not be realistic. Patients should also realize that multiple strabismus surgeries and prisms may be required.
Because of the restrictive myopathy of thyroid-associated orbitopathy, predominantly recessions, rather than resections, are performed. Whenever feasible, adjustable suture surgery is recommended. In patients intolerant of conscious suture adjustment, hang-back sutures can be adjusted using the corneal light reflexes. In select patients with thyroid-associated orbitopathy, strabismus surgery can be performed using topical anesthesia.

To prevent ocular ischemic syndrome, do not operate simultaneously on more than 2 muscles per eye.

Procedure considerations
Surgery of the inferior rectus muscle deserves special mention. Inferior rectus muscle recession may decrease upper lid retraction, but it also often results in lower lid retraction despite dissection of the lower lid retractors. Because the inferior rectus muscle has subsidiary actions (excyclotorsion and adduction), inferior rectus muscle recessions may lead to a component of intorsion and A-pattern strabismus.

If visualization during strabismus surgery is difficult, especially for the superior rectus muscle, a vertical lid split technique may be considered.

Botulinum toxin injections are used by some clinicians during the acute phase of thyroid-associated orbitopathy as a temporizing measure until orbital decompression can be completed. However, optic neuropathy following a botulinum toxin injection for strabismus in a patient with thyroid-associated orbitopathy has been reported.

Lid-Lengthening Surgery
If restoration of the euthyroid state does not improve lid retraction, consider lid-lengthening surgery. This surgery decreases corneal exposure and can be used to camouflage mild-to-moderate proptosis. In patients unwilling to consider lid surgery, possible alternatives to upper-lid lengthening include botulinum toxin injections to the upper lid and subconjunctival triamcinolone.

Lateral tarsorrhaphies can decrease upper and lower lid retraction, but the author does not prefer this method.

Amelioration of 2-3 mm of upper lid retraction can be done with a Müller muscle excision. Lateral levator tenotomy is often helpful to decrease the temporal flare. If further amounts of lid recession are required, levator recession can be considered.

Lower lid-lengthening usually requires a spacer material. Graft materials include human acellular dermis, tarsus, and conjunctiva from the upper lid, hard palate, and ear cartilage.
Horizontal tightening procedures (eg, lateral tarsal strip) increase scleral show in patients with proptosis.

In the horizontally tight eyelid, lateral canthal advancement is a useful adjunct to enhance the effect of retractor recession and reduction of temporal flare.
Blepharoplasty
Blepharoplasty is the last phase of restorative surgery in thyroid-associated orbitopathy (TAO). The transconjunctival approach to lower lid blepharoplasty can be used if no excess lower lid skin is present.

Upper lid blepharoplasty is performed transcutaneously with conservative skin excision. Brow fat resection may be considered. Dacryopexy may be required if lacrimal gland prolapse occurs.

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Intestinal Fistulae

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A fistula represents an abnormal communication between two epithelialized surfaces, one of which is a hollow organ .In the GI tract, a fistula may develop between any two digestive organs or between a hollow organ and the skin.

Acquired fistulas account for most GI fistulas and can be traumatic, spontaneous, or postoperative in nature.

More than 80% of enterocutaneous fistulas represent iatrogenic complications. In the past, acquired GI fistulas most commonly developed as a result of a difficult appendectomy. At present, they commonly occur as the result of anastomotic breakdown, dehiscence of a
surgically closed segment of stomach or bowel, unrecognizediatrogenic bowel injury following adhesiolysis, or during closureof a laparotomy incision.

Risk Factors

- Surgical procedures to treat cancer, inflammatory bowel disease (IBD), lysis of adhesions, or peptic ulcer disease
- IBD
- Diverticular disease
- Radiation
- Malignancy - Especially gynecologic and pancreatic
- Appendicitis
- Perforation of duodenal ulcers
- Abdominal trauma - Such as gunshot wounds, stabbing (sharp trauma), or motor vehicle accident (blunt trauma)
- Aortic aneurysm, infected aortic graft, or previous abdominal aortic surgery

Gastric Fistulas

Gastric fistulas are iatrogenic in most cases (85%). Gastric fistulas are uncommon and frequently occur after resection for cancer and less frequently after resection for peptic ulcer disease, necrotizing pancreatitis, an antireflux procedure, or bariatric surgery. Anastomotic leak after a gastric resection for cancer, peptic ulcer disease, or bariatric surgery can lead to leakage of intestinal or gastric juices, which initiates a cascade of events: localized infection, abscess formation, and, possibly, abscess and fistula formation.

Small Bowel Fistulas

Nearly 80% of small bowel fistulas result from complications of abdominal surgery. These fistulas may occur from disruption of the anastomotic suture line, inadvertent iatrogenic enterotomy, or small bowel injury at the time of closure. Inadequate blood flow from devascularization or tension at the anastomotic suture lines, anastomosis of diseased bowel, or perianastomotic abscess may compromise the integrity of surgical anastomoses.

Fistulas in Crohn Disease

Crohns disease, malignancy, peptic ulcer disease, and pancreatitis spontaneously cause 10-15% of small bowel fistulas. In patients with Crohn disease, fistulas arise from aphthous ulcers that progress to deep transmural fissures and inflammation, subsequently leading to adherence of the bowel to adjacent structures that eventually penetrate other structures. Microperforation with abscess formation leads to subsequent macroperforation into the adjacent organ or skin, resulting in fistula formation.

Crohn fistulas are more often internal and less commonly external (to the skin). Ileosigmoid fistulas, usually a complication of a diseased terminal ileum that invades the sigmoid colon, are the most common type of fistula between two loops of bowel. Enteroenteric, gastrocolic, duodenocolic, enterovesical, rectovaginal, and perianal fistulas are other potential complications of Crohn disease. Perianal fistulas are the most common external fistulas in patients with Crohn disease.

Colonic Fistulas

Colonic fistulas are primarily a consequence of intra-abdominal inflammation but can also occur after surgical intervention for an inflammatory condition.IBD, diverticulitis, malignancy, and appendicitis (especially with the presence of an appendiceal abscess requiring percutaneous drainage) are the most common inflammatory conditions that lead to colonic fistulas.

Pathophysiology

Anatomically, the fistula may be:

- *Internal* fistula: The communication occurs between two parts of the GI tract or adjacent organs. The tract of the fistula may erode into another portion of the intestines (enteroenteric fistula) or another hollow organ (enterovesical).
- *External* fistula: The communication involves the skin or another external surface epithelium. The tract may open into the body surface (enterocutaneous and pancreatic fistula) or vagina (enterovaginal fistula).
- *Mixed* fistula: describes an internal fistula associated with an external fistula.
- *Superficial* fistula drains on top of an open or granulating wound.
- *Deep* fistula: the tract traverses the abdominal cavity and drains onto the skin.

Physiologically, the fistula is classified as high or low output on the basis of the volume of discharge in 24 hours. Three different categories are recognized:

- *Low-output* fistulas: Enterocutaneous fistulas that drain less than 200 mL of fluid per day.
- *Moderate* output: Enterocutaneous fistulas thatdrain200 to 500 mL/24 hr.
- *High-output* fistulas: Enterocutaneous fistulas that drain more than 500 mL of fluid per day. The ileum is the site of the fistula in 50% of high-output fistulas.

Presentation

Patients with gastrocolic fistulas may present with symptoms of abdominal pain, weight loss, and feculent belching.

Enterovesical and colovesical fistulas are easier to diagnose in patients who present with symptoms of pneumaturia, fecaluria, and recurrent urinary tract infections.

Patients with rectovaginal and anovaginal fistulas may be asymptomatic and present with symptoms only when the bowel movements are more liquid. Possible symptoms include inadvertent passage of stool or gas, dyspareunia, and perineal pain.

Patients with external fistulas generally present with symptoms of drainage through the skin. Patients with aortoenteric fistulas may report rectal bleeding.

Symptoms caused by fistulas that involve 2 segments of the bowel vary depending on the location of the fistula and the amount of bowel bypassed. For this reason, enteroenteric fistulas in which only a short segment of bowel is bypassed may be asymptomatic and diagnosed incidentally based on imaging findings or during surgery.

Conversely, enterocutaneous fistulas may be associated with a triad of sepsis, fluid and electrolyte imbalance, and malnutrition. Iatrogenic enterocutaneous fistulas usually become clinically evident between the fifth and tenth postoperative days and may not be progressing as expected. Fever, leukocytosis, prolonged ileus, abdominal tenderness, and wound infection are the initial signs. The seriousness and severity of these manifestations depend on the surgical anatomy and physiology of the fistula. Sepsis is a prominent feature of postoperative intestinal fistulas and is present in 25% to 75% of cases. Sepsis is the result of diffuse peritonitis or localized abscess, abdominal wall or necrotizing infection, or contamination of a sterile hollow organ with intestinal contents.

Loss of intestinal contents through the fistula results in hypovolemia and dehydration, electrolyte and acid-base imbalance, loss of protein and trace elements, and malnutrition. In a high intestinal fistula, it also results in loss of the normal inhibitory effect on gastric secretion, thus resulting in a gastric

hypersecretory state. With high-output enterocutaneous fistulas, there is also intrahepatic cholestasis related to the loss of bile salts, disruption of enterohepatic circulation, and bacterial overgrowth in the defunctionalized intestine. Malnutrition results from loss of protein-rich secretions, lack of nutrient intake, loss of absorption caused by bypass of the gut (e.g., gastrocolic, duodenocolic, high enterocutaneous fistulas), and sepsis that sets the stage for nutritional deficiency and rapid breakdown of body muscle mass.

In gastroduodenal and proximal small bowel fistulas, the output is high and the fluid loss, electrolyte imbalance, and malabsorption are profound. In distal small bowel and colonic fistulas, the output is low and dehydration, acid-base imbalance, and malnutrition are uncommon. Significant electrolyte imbalance occurs in 45% of patients and malnutrition occurs in 55% to 90%.

Skin and surgical wound complications develop as a result of contact of GI effluent with skin or the wound. Effluent dermatitis results from the corrosive effect of intestinal contents, which cause irritation, maceration, excoriation, ulceration, and infection of the skin. Fecal dermatitis is marked by erythema and desquamation and may encourage skin sepsis. Superficial and deep surgical wound and necrotizing infections also develop. Pain and itching by contact of effluent with unprotected skin is intolerable and affects the morale of the patient.

Diagnosis and Management

In the past, the main focus of management involved suctioning of the intestinal effluent and early surgical intervention. This approach has proven ineffective and is associated with significant patient morbidity and mortality and a high reoperation rate. At present, management requires the involvement of a surgeon, nutritionist, enterostomal therapist, interventional radiologist, and gastroenterologist; it entails initial medical treatment to allow spontaneous healing of the fistula, early surgical intervention in a select group of patients, and planned definitive surgery for patients whose fistulas have failed to heal.

External intestinal fistulas result in prolonged hospital stays and enormous cost to the hospital and are associated with significant patient disability, morbidity, and mortality (6% to 30%). Although spontaneous closure occurs in 40% to 80% of cases, operative intervention may be required in 30% to 60% of cases. The first step in the management of a GI fistula is to prevent its occurrence. Reducing the likelihood of an anastomotic leak requires adherence to sound surgical principles and proper techniques. Should a fistula form, management involves several phases that are applied systematically and simultaneously.

The treatment of enterocutaneous fistulas should proceed through an orderly sequence of steps.

1. Stabilization. Fluid and electrolyte resuscitation is begun. Nutrition is provided, usually through the parenteral route initially. Sepsis is controlled with antibiotics and drainage of abscesses. The skin is protected from the fistula effluent with ostomy appliances or fistula drains.
2. Investigation. The anatomy of the fistula is defined using the studies described below.
3. Decision. The available treatment options are considered, and a timeline for conservative measures determined.
4. Definitive management. This entails the surgical procedure, and requires appropriate preoperative planning and surgicalexperience.
5. Rehabilitation.

Stabilization

Once a leak is diagnosed or suspected, management involves resuscitation, TPN, correction of electrolyte imbalances, and transfusions as appropriate.

- Oral intake is stopped and the bowel is put at rest, thus decreasing luminal contents and reducing GI stimulation and secretion. An NG tube is placed if obstructive symptoms are present. Routine NG placement is not helpful and subjects the patient to complications, such as sinusitis and aspiration.
- Broad-spectrum IV antibiotic therapy is started and later adjusted according to cultures.
- H2 antagonists or PPI helps decrease peptic ulceration and may decrease fistula output but does not aid in the closure of the fistula.
- Accurate measurement of output from all orifices and the fistula is paramount in maintaining fluid balance.

Control of Sepsis
It is important because continued sepsis is a major source of mortality that results in a state of hypercatabolism and the failure of exogenous nutritional support to restore and maintain body mass and immune function; it is also associated with a decreased rate of healing of GI fistulas.

Infected surgical wounds are opened and drained, abdominal wall abscesses are incised and drained, and intraabdominal fluid collections are drained percutaneously or surgically. Percutaneous drainage is tolerated better and allows changing a complex fistula (fistula associated with an abscess) to a simple fistula that has a better chance of spontaneous closure. A small pigtail catheter may be changed to a larger catheter that allows irrigation of the abscess cavity, later injection of contrast to assess resolution of the abscess, and study of the anatomy of the fistula.

Nutrition
It is one of the most important factors contributing to a successful outcome in the management of intestinal fistulas. TPN must be started early after the correction of electrolyte imbalance and repletion of volume. TPN allows bowel rest, which decreases output, eliminates negative nitrogen balance, improves the patient's nutritional status, allows better timing of the operation when needed, increases the rate of recovery, and may slightly improve the closure rate once sepsis is controlled. Trace elements, multivitamins, vitamin K, and medications such as octreotide may be added to the TPN. TPN is the initial nutritional support for any patient with a fistula and is continued in patients with high-output fistulas or patients who cannot tolerate oral intake.

Fistuloclysis
Enteral nutrition (low-residue diet, elemental diet, liquid whole protein diet) is administered to patients with low-output small bowel and colonic external fistulas. Fistuloclysis (i.e., infusion of nutrition directly through the fistula into the bowel distal to the fistula) is another option to deliver enteral nutrition to patients whose fistula has not healed spontaneously, provided there is more than 75 cm of healthy bowel distal that is in continuity with the fistula. Fistuloclysis is safer and less expensive than TPN and prevents atrophy of the bowel distal to the fistula.

Peristomal Skin Protection
Early control of fistula output is essential to protect the perifistula skin from the corrosive effects of intestinal effluent, promote healing of damaged skin and surgical wounds, and facilitate nursing care of the patient. Early involvement by an enterostomal therapist and wound care team cannot be overemphasized. Protection of the skin is achieved with barriers, sealants, adhesives, and pouches.

Negative-Pressure Wound Therapy
It is another treatment strategy whereby the continuous suction of fistula output minimizes contact between intestinal contents and surrounding tissue. Hence, it protects perifistula skin, reduces the need for dressing changes, promotes wound healing, and even accelerates fistula closure, especially in deep fistulas. Closure has been reported to occur in 46% to 84% of cases.

Somatostatin (SMS) analogues
Octreotide is an inhibitory hormone consisting of 2 peptides (14 amino acids and 28 amino acids in length) secreted by hypothalamus and delta cells of the stomach, intestines, and pancreas. It inhibits the release of growth hormone (GH) and thyroid-stimulating hormone (TSH) and suppresses the release of many GI hormones (gastrin, cholecystokinin, secretin, motilin, vasoactive intestinal polypeptide [VIP], glucose-dependent insulinotropic polypeptide [GIP]).

Octreotide, with a long half-life help in management of the fistula by reducing GI secretions and inhibiting GI motility, thus controlling and reducing its output. Their value in healing intestinal fistulas is yet to be proven and routine use is limited because they are not without side effects. Somatostatin leads to cellular apoptosis, villous atrophy, and interruption of intestinal adaptation, and may be associated with acute cholecystitis.

Investigations

Once initial sepsis is controlled, nutrition provided, and wound and fistula care provided, studies are performed to define the surgical pathology of the fistula (origin, course, length of the fistula) and condition of the bowel (presence of intrinsic intestinal disease, presence of distal obstruction, continuity of the bowel) and to evaluate resolution of the intra-abdominal abscess.

Fistulogram
It is performed by injecting a water-soluble contrast medium or barium through an existing drain or by inserting a 5 Fr pediatric feeding tube or a Foley catheter into the external opening of the fistula. A fistulogram delineates the anatomy of the fistula and identifies associated cavities, other fistulas, and distal obstructions.

Contrast Enema
It demonstrates the presence of a colocutaneous fistula in 90%, a colovesical fistula in 34%,and a coloenteric fistula in most cases.

Cystoscopy
It identifies the fistula opening in 40% of enterovesical fistulas but the findings of localized bullous edema, with erythema and possible ulceration, are suggestive of the diagnosis in most patients.

Endoscopy or Colonoscopy
This can be helpful in determining the origin of the bowel disease that caused the fistula, but it is not a particularly helpful or necessary study to reveal a fistula. Biopsy samples may be obtained during the procedure and are useful in diagnosing IBD or Crohn disease and malignancy.

Dye Injection
Instilling methylene blue into the rectum and examining a vaginal tampon 15 minutes after placement can often establish the presence of a rectovaginal fistula.

Ultrasonography
Ultrasonography can be used in conjunction with physical examination to identify abscesses and fluid collections along the fistula tract.

Barium Enema and Small Bowel Series
Contrast studies to evaluate the stomach, small intestine, and colon may reveal a fistula and may also be helpful in determining the cause of fistula formation by identifying diverticular disease, Crohn disease (characteristic string sign), or evidence of malignancy.

CT scan
It allows evaluation for the resolution of intra-abdominal abscesses and presence of intrinsic intestinal disease. Leakage of contrast material from the intestinal lumen can be observed. Intra-abdominal abscesses should be sought and drained percutaneously. CT scanning often reveals perifistular inflammation. This provides additional information regarding the possible etiology of the fistula and the extraluminal involvement of disease. CT angiography may be used in the diagnosis of suspected aortoenteric fistulas if the patient is stable.

MRI
Although magnetic resonance imaging (MRI) is reported as an imaging modality that can help identify and characterize enteric fistulas, motion artifact may limit its usefulness, and MRI is not considered a routine adjunctive study in the evaluation of patients with enteric fistulas. T1-weighted images provide information relative to the inflammation in fat planes and possible extension of the fistula relative to the surrounding visceral structures. T2-weighted images can demonstrate fluid collections along the fistula tract and inflammatory changes within the surrounding muscle.

Decision and Definitive Management
With such an orchestrated approach, most external fistulas heal spontaneously. Factors associated with spontaneous healing or failures to close are:

- Poor nutrition
- Medications such as steroids
- Malignant fistula
- Fistula related to Crohn's disease
- Fistula in radiated fields
- Fistula site :Gastric, Duodenal
- Persistence of local inflammation and sepsis
- Presence of a foreign body (e.g., meshes or sutures)
- Epithelialization of fistula tract
- Fistula tract <2 cm
- Distal obstruction to the fistula site

A useful mnemonic designates factors that inhibit spontaneous closure of intestinal fistulas: "FRIEND" (**F**oreign body within the fistula tract, **R**adiation enteritis, **I**nfection/Inflammation at the fistula origin, **E**pithelialization of the fistula tract, **N**eoplasm at the fistula origin, **D**istal obstruction of the intestine)

After control of sepsis, approximately 60% to 90% of external intestinal fistulas with favorable factors will close spontaneously with medical management, 90% will close within 4 to 6 weeks, and less than10% in months 2 and 3. There are limited therapeutic options for enterocutaneous fistulas (ECFs) that fail to close—accept the fistula as a stoma awaiting optimal time for definitive closure or attempt direct closure.

Direct repair is applicable to a superficial bud fistula whereby limited dissection is performed to identify and close the edges of the fistula extraperitoneally and protect the suture line with a biologic dressing, with or without tissue adhesive. Although several attempts may be required to achieve successful closure of the fistula, the surgery is a local low-risk procedure and can be repeated.

Definitive repair requires careful planning and may be a daunting task. Definitive closure requires a waiting period of 8 to 12 weeks, and requires that sepsis be controlled, nutrition provided, and skin is protected. The waiting period is crucial to allow recovery of immunologic competence, improvement of nutritional status, and resolution of the period of dense inflammatory reaction. There are no well-established guidelines to help in determining the timing of surgery. However, the experience of the surgeon, general condition of the patient, softness of the abdominal wall and abdominal cavity, and surgical anatomy of the fistula must be taken into consideration. A dense intra-abdominal inflammatory reaction occurs 10 to 21 days after surgery and lasts for 6 to 8 weeks before starting to resolve.

A simple fistula—single fistula with direct communication between the bowel and skin, a short tract and small enteral opening, and associated with other favorable factors—can be closed 12 weeks after the index surgery. A complex fistula—a fistula with a long tract and associated with other internal fistulas, large abscess cavity, fistula that opens into the base of a disrupted wound, or other unfavorable factors—is closed 6 to 12 months after the index surgery. Complex fistulas associated with intrinsic intestinal disease require definitive surgical intervention once the initial sepsis is controlled because spontaneous closure is highly unlikely and extirpation of the diseased bowel is essential.

A controlled ECF that opens into the base of an interrupted wound requires abdominal wall construction at the time of definitive repair of the fistula. The fistulizing segment must not be excluded or bypassed to avoid the risk of blind loop syndrome. The fistula is excised, continuity of the GI tract reestablished, and the freshly constructed anastomosis wrapped with omentum, if available. Gastric, duodenal, and proximal jejunal fistulas that cannot be resected without a major surgical procedure are best managed with a Roux-en-Y intestinal anastomosis. The laparotomy incision is closed primarily or with durable well-vascularized coverage. Autogenous tissue reduces the risk of infection. Pedicle or free flaps with microvascular reconstruction may be considered; however, component separation when the rectus muscle is intact, with or without augmentation with acellular dermal matrix or synthetic mesh, is the preferred procedure.

Postoperative morbidity, ventral hernia formation, and recurrent ECFs develop in approximately 20% to 25% of cases. Biologic material (e.g., acellular human or porcine dermal matrix, porcine submucosa) used for visceral overlay protection or reconstruction is another viable option in this setting of compromised operative field because the implant resists infection and, when postoperative infection occurs, removal of the implant is not necessary. However, the product is expensive and the procedure is associated with a high rate of hernia formation and abdominal wall laxity. Occasionally the incision is closed in stages. The incision may be left open (laparotomy), an absorbable mesh (polyglactin or polyglycolic acid) may be used to bridge the fascial defect, or negative-pressure wound therapy can be instituted. Once granulation tissue is formed, a split-thickness skin graft is applied. New innovative approaches, such as transcatheter injection of diluted thrombin, endoscopic tissue sealant or clip application, and porcine small intestinal submucosa have been used in recalcitrant cases or as adjunctive therapy to hasten healing of the intestinal fistula, with some success.

The overall objectives are to increase the probability of spontaneous closure. Nutrition and time are the key components of this approach. Most patients will require TPN; however, a trial of oral or enteral

nutrition should be attempted in patients with low-output fistulas originating from the distal intestine. The somatostatin analogue octreotide is a useful adjunct, particularly in patients with high-output fistulas; its administration reduces the volume of fistula output, thereby facilitating fluid and electrolyte management. Further, octreotide may accelerate the rate at which fistulas close; however, its administration has not clearly been demonstrated to increase the probability of spontaneous closure.
In patients with Crohn's disease, infliximab (Remicade) may also be used to aid in closure of the fistula in a select group of patients.

Outcomes

Enterocutaneous fistulas are associated with a 10 to 15% mortality rate, mostly related to sepsis or underlying disease. Surgery for fistulas is associated with a greater than 50% morbidity rate, including a 10% recurrence rate.

Current management of CBD stones

Anubhav Vindal, Jagdish Chander

During the era of open cholecystectomy the management of common bile duct stones (CBDS) was relatively straightforward, but with the advent of laparoscopic cholecystectomy (LC) in 1980s, the treatment of CBDS, whether recognized preoperatively or peroperatively remains controversial. Treatment options include selective preoperative endoscopic retrograde cholangiopancreatography (ERCP), open choledochotomy, intraoperative ERCP with endoscopic sphincterotomy (ES), postoperative ERCP with ES, and single stage laparoscopic clearance of CBD stones.

History

In first part of the 19th century, surgery of the biliary system consisted of attempts to duplicate what nature had shown to be effective treatment: creation of cutaneous fistulas and delayed enteric fistulas. The introduction of ether anaesthesia in 1846 ushered in the era of modern biliary surgery and the first successful removal of a gallbladder. It was not until 1890 that the first surgical exploration of the common bile duct (CBD) was performed by a Swiss Surgeon, Ludwig Courvoisier, who removed a gallstone via an incision in the CBD, 8 years after Langenbuch reported the first cholecystectomy.[1]

Then Thorton and Abbe reported their experiences with direct incision into the CBD to remove calculi.[2] The next important milestone was the introduction of intraoperative cholangiography in 1932 by Mirizzi.[1] This procedure resulted in two effects. First, it reduced unnecessary bile duct explorations. Second, it reduced the incidence of retained stones, which was associated with high reoperative mortality.

The introduction of endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (ES) by gastroenterologists from Germany and Japan in the 1970s, led to a revolution in the treatment of CBDS. This method soon became the treatment of choice for managing choledocholithiasis.[2]

Berci was pivotal in the development and dissemination of first the rigid, and later the flexible, choledochoscopy.[1] By the 1980s, the use of intraoperative choledochoscopy was widely disseminated and proven to reduce retained stones in an additional 10% to 15% of patients that otherwise would have been missed.[3,4]

All was well in the world of biliary surgery until 1989, and the treatment of CBD calculi was relatively straightforward. Patients suspected of harbouring CBD stones underwent intraoperative cholangiography. If CBD calculi were discovered, the bile duct was opened and the stones retrieved. If there were too many or they could not all be retrieved, a biliary enteric anastomosis was performed.

The biliary world turned upside down with the introduction of therapeutic laparoscopy. Preoperative diagnostic endoscopic retrograde cholangiography (ERC)/endoscopic sphincterotomy (ES) became the standard for patients suspected of having choledocholithiasis to avoid conversion to open CBD

exploration (CBDE). Postoperative ES became the preferred approach for the treatment of common duct stones encountered at surgery or discovered afterward.[5,6]

Efforts to treat patients with common duct stones in one session and avoid the potential complications of ES (especially in younger patients with small-diameter CBDs) resulted in several laparoscopic techniques of trans cystic CBD exploration (LTCBDE) including lavage, trolling with wire baskets or biliary balloon catheters, cystic duct dilation, ampullary balloon dilation, biliary endoscopy, and stone retrieval with wire baskets under direct vision, even antegrade sphincterotomy and lithotripsy. Almost concurrently in 1990s, the technique of laparoscopic CBD exploration using a choledochotomy was also described.[6] This technique was the laparoscopic replica of the open procedure that many surgeons were well versed with. The trans choledochotomy approach was especially useful in cases where the stone size was too large, or the stones were too many or the cystic duct morphology was unfavourable for the trans-cystic route.

Incidence

Common bile duct stones are a fairly common entity. Between 3% to 18 % of patients undergoing Laparoscopic Cholecystectomy (LC) for gallbladder stones have synchronous CBD stones.[7,8]

Clinical presentation

The symptoms and signs of CBDS are highly variable and can range from patients being completely asymptomatic, to complications such as cholangitis or pancreatitis.[9]

The prevalence of asymptomatic CBDS has been found to be between 5.2% and 12%.[10] A common presentation of CBDS is the biliary colic. Pain is often situated in the right hypochondrium or epigastrium and can last from 30 minutes to several hours, with associated symptoms such as nausea and vomiting. Other common symptoms include jaundice along with pale stools and dark-coloured urine.[9]

Two serious complications of CBDS are cholangitis and gallstone pancreatitis. Acute obstructive cholangitis is a life-threatening complication caused by an infection of the biliary ductal system secondary to biliary obstruction.[9] In cholangitis, the classic symptoms of Charcot's triad may be encountered, and the less common Reynold's pentad adds to the diagnosis.[9] Despite the advancement in treatment, acute obstructive cholangitis still carries a mortality rate of 10–20% .[11]

Diagnostic investigations

The preoperative evaluation for CBD stones should include a careful history, biochemical tests and abdominal ultrasonography. It seems reasonable to avoid further diagnostic preoperative investigations and routine intraoperative cholangiography in patients with absence of jaundice, normal liver function tests, and ultrasonographic evidence of a normal biliary tree (CBD diameter <9 mm).[12]

However, investigation of the group at risk is necessary. If there is any suspicion that preoperative choledocholithiasis is present, magnetic resonance cholagio pancreatography (MRCP) or endoscopic retrograde cholangio pancreatography (ERCP) is performed. ERCP should be performed only in patients who are expected to require an intervention; it is not recommended for use solely as a diagnostic test.[12]

Laboratory Tests

Patients exhibiting the symptoms described above require diagnostic investigations to assess for the presence of CBDS.[13] Liver function tests (LFTs) can be used to screen for CBDS. Elevated serum bilirubin and alkaline phosphatase typically reflect biliary obstruction, but these are neither highly sensitive nor specific for CBDS.[14] Various studies have proven elevated serum gamma glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) to be the most frequent abnormalities in laboratory values of patients with symptomatic CBDS.[9] Most of the studies have shown that laboratory studies must be used in addition to imaging modalities to predict the likelihood of CBDS.[14]

Imaging Modalities

Transabdominal Ultrasonography (TAS)

It is the first line investigation in patients with suspected CBDS.[9] Its sensitivity for detecting CBDS is between 25% to 63%, with a specificity of approximately 95% depending on the degree of dilation of the CBD and investigator's experience.[9,13]

Endoscopic Retrograde Cholangio Pancreatography (ERCP)
ERCP is often described as the gold standard test to for the detection of CBDS. This procedure was initially used primarily in diagnosis, but today is more commonly used as a therapeutic modality.[13] ERCP has sensitivity between 90% to 95% in detecting CBD stones and a specificity of 92% to 98%.[13,15] Christensen et al. demonstrated that the ERCP has a morbidity rate of 15.9% and a mortality rate of 1%.[16]

Percutaneous Transhepatic Cholangiography (PTC)
It is an invasive procedure where the intra hepatic biliary system is cannulated under radiological guidance followed by instillation of dye through a percutaneously placed needle. It is not a routine initial diagnostic test in patients with CBD stones but is the modality of choice in patients with previous gastric surgery, distal obstructing CBDS that failed ERCP or in patients with cholangio hepatitis and extensive intrahepatic stone disease.[17]

Endoscopic Ultrasound (EUS)
It involves the endoscopic insertion of an ultrasound probe through the stomach and up to the second half of the duodenum, allowing for ultrasound images of the CBD without the interference of subcutaneous fat and bowel gas.[18] It allows application of the ultrasound transducer directly against the luminal surface, thereby enhancing image quality. The proximity of the transducer to the target tissue also permits the use of higher frequency ultrasound, which further contributes to the enhanced image resolution. Sensitivity of EUS varies from 95 – 97%, while specificity is between 95 – 98%.[18,19] EUS is significantly more sensitive than TAS in detecting CBD stones. Its sensitivity is comparable to the diagnostic ERCP, while its major advantage is a significantly decreased morbidity compared to ERCP.[18]

Magnetic Resonance Cholangio Pancreatography (MRCP)
It has emerged as an accurate, non-invasive diagnostic modality for investigating the biliary ducts.[20] It may be especially beneficial in identifying patients who would benefit from early intervention.[12] A meta-analysis of 67 published controlled trials shows that MRCP has an excellent overall sensitivity of 95% and a specificity of 97% for demonstrating CBDS.[21] Some major disadvantages of MRCP, as compared to ERCP, are the lower spatial resolution, potential for claustrophobia, and the inability to evaluate patients with pacemakers or ferromagnetic implants.[20,21]

Intra Operative Cholangiography (IOC)
This technique involves instillation of contrast into the biliary tree through the cystic duct, and the visualization is done using fluoroscopy. The routine use of IOC is still controversial. Some authors supporting routine IOC, while others favour selective IOC, and others report no advantages in IOC with respect to missed CBD stones.[12] However, it can be an useful tool to identify choledochal stones.[12] This procedure can be performed during open or laparoscopic cholecystectomy. IOC has a sensitivity of 98% and specificity of 94% to detection of CBDS.[22] IOC can fail primarily due to inability to cannulate the cystic duct, leakage of contrast fluid during the injection, air bubbles mimicking stones, failure to fill the biliary tree because of too rapid contrast injection into the duodenum, and spasm of the sphincter of Oddi. Reports have shown that this procedure ensures fewer retained stones, fewer postoperative ERCPs, and a reduction in the number of CBD injuries.[9,12,22] One drawback is lengthening of the operative time by approximately 15 minutes.[12,22]

Intra Ductal Ultrasonography (IDUS)
The technical evolution of EUS has lead to the development of small calibre intra ductal ultrasound (IDUS) mini probes (about 2 mm), which can be passed through standard endoscopes directly into the bile or pancreatic duct. The small calibre, flexibility, and excellent image quality produced by these catheters makes them ideal for evaluating a variety of biliary disorders. IDUS is capable of producing better image resolution than standard endoscopic ultrasound. Acoustic coupling is optimized by the tubular anatomy of the bile duct, which is fluid filled and only slightly larger in calibre than the probe itself. In addition, the probes operate at higher frequencies (12 to 30 MHz) than standard EUS, which leads to higher image resolution. Although the utility of intra ductal ultrasonography (IDUS) for common bile duct stones has been reported, the clinical significance of this procedure in making therapeutic decisions has not been well clarified.[23] IDUS is a valuable method for residual small stones in the common bile duct after endoscopic lithotripsy.[23,24] IDUS increases sensitivity and specificity in the diagnosis of choledocholithiasis, and these gains are not translated into a notable

increase in procedure time (7–15 minutes).[24] IDUS is especially recommended in patients who have a dilated bile duct with suspected small bile duct stones when ERCP is not diagnostic.[24]

Management options

No consensus exists regarding the ideal management of gallbladder and CBD stones. CBD stones can be detected preoperatively, intra operatively or postoperatively. Consequently the management options are quite varied especially in the present era of advanced laparo endoscopic techniques.

The following management strategies are available:

- Endoscopic Sphincterotomy (ES) with stone extraction followed by laparoscopic cholecystectomy.
- Simultaneous endoscopic stone extraction with laparoscopic cholecystectomy
- Combined laparoscopic cholecystectomy and CBD exploration (LCBDE)
- Open CBD exploration
- ES post cholecystectomy

Other methods include electrohydraulic lithotripsy (EHL), extracorporeal shockwave lithotripsy (ESWL), laser lithotripsy, and dissolving solutions that are indicated only in special situations.

Every procedure has its advantages and disadvantages and there is a broad overlap between the indications for an ideal management option in a particular clinical scenario. Therapeutic decision making is based on the local availability of expertise. Two groups of interventions have significant roles in management of CBD stones:

(1) Pre or post operative ERCP with endoscopic biliary sphincterotomy (ES) in a two-stage procedure,
(2) Surgical bile duct clearance and cholecystectomy as one stage procedure – open or laparoscopic.

Several randomized controlled trials showed similar effectiveness for both methods of treatment.[25,26] It has been reported that one-stage management of symptomatic CBDS is associated with less morbidity and mortality (7% and 0.19%) than two-stage management (13.5% and 0.5%).[26]

Open CBDE

Open exploration for CBD stones was the traditional treatment for management of this disorder. However, with the advent of laparoscopic surgery in general, and laparoscopic CBD exploration in particular, fewer than ever procedures are being done through the open approach worldwide.[27] The advantages offered by the laparoscopic approach over the open approach include, among many others, lesser postoperative pain and discomfort for the patient, faster postoperative recovery and significantly shorter hospital stay. The patients are able to return to the activities of daily living much faster compared to the open technique. However, there still remain few situations in which the open route is preferable over the laparoscopic approach, and these include non availability of the expertise/equipment, unfavourable biliary anatomy, large impacted stones in the CBD and other general contraindications to laparoscopic surgery.[12,27]

Pre operative ERCP

The success rate for stone clearance is 87% to 97% but up to 25% of patients require two or more ERCP treatment.[28] The associated morbidity and mortality rates are 5% to 11% and 0.7% to 1.2% respectively. Moreover, ERCP is not possible in 3% to 10% of all patients.[26] Complications of ERCP include bleeding, duodenal perforation, cholangitis, pancreatitis and bile duct injury.[26,28] Schreurs et al. showed 75%–84% patients undergoing ERCP/EST had no symptoms with up to 70-month follow up.[29]

Intraoperative ERCP

It is another option for removal of CBDS, particularly stones in the common hepatic duct or intrahepatic system. The use of intraoperative ERCP is effective but is associated with logistic and technical difficulties. It requires additional equipment and additional personnel availability in the OT during the procedure. The patient's position may be suboptimal for the endoscopist to perform endoscopy, identify the papilla and cannulate it.[26,28]

Postoperative ERCP

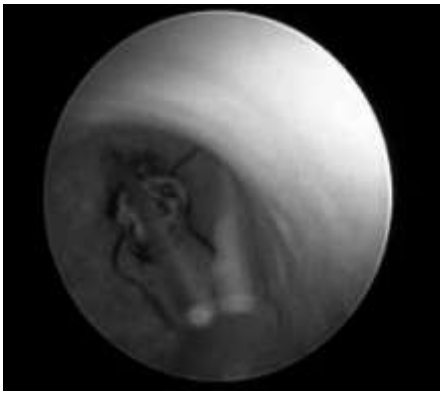
Postoperative ERCP is done for intra operatively diagnosed CBD stones during laparoscopic cholecystectomy when the expertise to perform laparoscopic CBD exploration is not available. The

patients are usually taken up for ERCP in the same admission and the success rates of removal of stones vary from 55 to 80%.[28] However, the dangers include all the complications of ERCP and the dilemma of managing CBD stones in ERCP failure because a third procedure would then be needed.[26,28]

Laparoscopic CBD exploration

Laparoscopic exploration of the CBD via the trans cystic route was first reported in 1991.[1,2] Laparoscopic choledochotomy and CBD exploration also was first reported in 1991 but has been less widely documented.[2] Berci and Morgenstern, in the multi-institutional SAGES study, documented the procedure for laparoscopic extraction of CBDS in 1994.[30] In 1999, Cuschieri et al. in the EAES study concluded that the laparoscopic single-stage approach for management of gallstone disease and choledocholithiasis is the preferable option in fit patients[31]. However, the dissemination of this procedure has been limited.

For the trans cystic exploration, a balloon angioplasty catheter (8 Fr) is used to dilate the cystic duct and CBD stones are visualized using either IOC and fluoroscopy or direct visualization using a choledochoscope. CBD stones are removed using trolling with wire baskets or balloon catheters or flushed into duodenum by saline lavage.[30]



For the trans choledochal route, a choledochotomy is made in the supra-duodenal part of the CBD. Intraoperative choledochoscopy is usually performed to visualize and remove the CBDS under vision and to check for the completion of removal at the end of the procedure. An additional 5-mm port inserted at the highest point in the epigastrium in the right paramedian position for choledochoscopy of the lower CBD.[32] The calculi are extracted by using a Dormia basket under choledochoscopic vision. Impacted stones can be broken under direct vision using intracorporeal lithotripsy with Holmium laser, and the fragments can be flushed through the ampulla into the duodenum with hydrostatic pressure.[32]

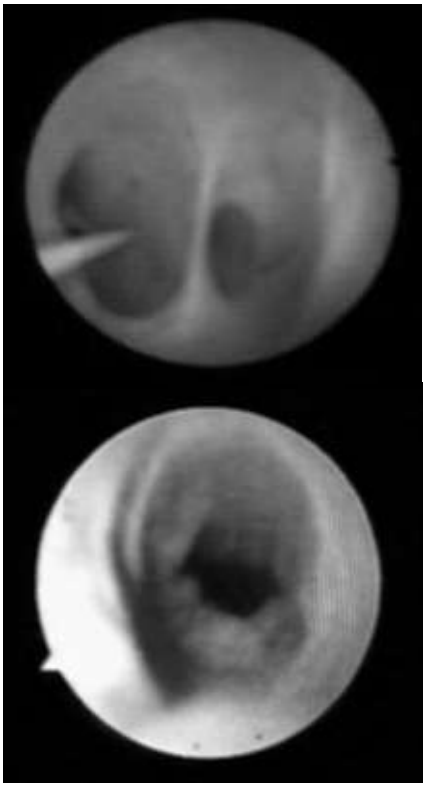
Closure of the CBD can be done in several ways depending on the merits of each case. In case of concern of residual debris, extensive inflammation, or manipulation or spasm of the ampulla, closure over a drainage tube is preferred. This can either be in the form of an external drainage (T-tube), or internal drainage (endo-biliary stent).[32] In cases with no residual debris or any inflammation of the CBD primary closure of the duct without any drainage is preferred. Choledochotomy is generally closed using continuous sutures of 4-0 polygalactin, although some surgeons may prefer an interrupted closure.[32] For CBDs > 20 mm in size and/or impacted CBD stones, laparoscopic choledochoduodenostomy is preferred creating a stoma of at least 20 mm, using single layer of interrupted sutures of 3-0 polygalactin.[32,33]

The successful laparoscopic management of CBDS is dependent on several factors including surgical expertise, adequate equipment, the biliary anatomy and the number and size of CBD stones. Successful stone clearance rates for LCBDE range from 85% to 95% with a morbidity rate of 4% to 16% and mortality of 0% to 2%.[32,34] A metanalysis of 1762 patients who underwent LCBDE from 19 studies worldwide showed a mean duct clearance of 80% with average morbidity of <10% (4–16%) and mortality of <1% (0–2.7%).[35] Also, trans cystic stone clearance may have a recovery very similar to laparoscopic cholecystectomy alone as it is a more anatomical approach.[34,35]

Laparoscopic trans cystic common bile duct exploration (LTCBDE) vs laparoscopic choledochotomy[32]

	LTCBDE	**Lap choledochotomy**
Skill	Endoscopy	Lap suturing
Stones (number)	<8	Any number
Stone Size (mm)	<9	Any size
Stone Location	Distal to cystic duct	Entire duct
CBD diameter (mm)	Any	>9
Drain	Optional	Suggested

Contraindication	Friable cystic duct Intrahepatic stones Multiple, large stones	Small-diameter CBD
Advantages	No T-tube Shorter hospital stay Quick	T-tube for postop access
Disadvantages	Equipment Intensive new skills required	Lap suturing T-tube



In our series of laparoscopic CBD exploration, which is the largest such series published from south east Asia, the majority of patients had stones between 5 to 15 mm.[32] As a result of the large average stone size and number trans choledochal route was used in the majority of patients. The average duration of surgery was 139.9 ± 26.3 (range, 90–205) min and the conversion rate is 4% which is one of the lowest reported in the published literature.[32] Fifteen percent of our patients had nonfatal postoperative complications ranging from wound infection, transient hyper-amylasemia, bile leakage, intra-abdominal collection, and upper gastrointestinal hemorrhage. There were three cases of retained stones (2%), all of which were managed effectively with postoperative ERCP. Postoperative stay ranged from 2 to 33 days with an average of 4.6 ± 4.1 days. Eighty-one percent of the patients had a stay of 5 days or less.[32]

The ideal method of CBDS removal is the one that does not cause injury to the sphincter of Oddi, because it is desirable to preserve the sphincter in patients younger than aged 60 years.[32,36] One-stage management of CBDS with LC and LCBDE has lowest morbidity and mortality and is cost-effective with a short hospital stay.[27] It treats both gallstones and CBDS in single stage compared with staged procedures, and can be performed as a day care procedure.[27,35] LCBDE also preserves the function of sphincter of Oddi and hence reflux-related complications, such as cholangitis and recurrent stones associated with sphincter damage, are not seen.[32,36] The mean number of procedures needed per patient for complete clearance of CBDS has been reported as 1.46 with ERCP ± ES and 1.23 with LCBDE.[26,31]

Extra corporeal Shock Wave Lithotripsy (ESWL)

ESWL was first used for treating gallstones in 1980s following its successful use in fragmenting renal calculi.[9] ESWL involves the percutaneous administration of sound waves directed at the liver and bile duct. It is not performed during endoscopy, but rather before an ERCP in hopes of shattering large stones into smaller, more manageable fragments. European studies evaluating ESWL report duct clearance rates of 83% to 90%, but its acceptance elsewhere has been slow.[9,12]

Dissolution techniques

These solutions are instilled either directly into the biliary tree or are administered orally, absorbed by GIT and then secreted in the bile. They do not cause irritation of the biliary tree and are not toxic. Every dissolution therapy will last for several weeks, therefore the ideal solvent has not yet been produced.[37] The use of urso-deoxy-cholic acid (UDCA) and cheno-deoxy-cholic acid has only been shown to dissolve cholesterol-containing stones. Approximately 85– 95% of patients in the west will have cholesterol stones. Continuing therapy with UDCA appeared to prevent recurrence of gallbladder microlithiasis.[9] Methyl-Tert-butyl-Ether (MTBE) is an excellent cholesterol solvent that has been shown to work faster, but it is toxic to liver and duodenal mucosa. It has been proposed by several studies that using dissolution in combination with endoscopic retrieval or lithotripsy has better outcomes.[9,12,37]

Percutaneous extraction

This technique is used for non operative extraction of CBD stones when ERCP has failed or has not been possible due to an altered anatomy and an inaccessible papilla. As a preliminary procedure, a

percutaneous trans-hepatic cholangiography is performed and stones are visualized. Percutaneous trans-hepatic balloon dilation of the papilla of Vater is then performed and the stones are pushed out into the duodenum using a Fogarty balloon catheter.[38] If the stone diameter is larger than 15 mm, then basket lithotripsy is performed before balloon dilation. The procedure has a success rate of 80 - 96% in CBD stones and in 55 - 61.5% in intra hepatic stones.[38] Complications described for this procedure include cholangitis, subcapsular biloma, subcapsular hematoma, subcapsular abscess, bile peritonitis, duodenal perforation and CBD perforation.[38]

Endoscopic versus laparoscopic removal

Endoscopic methods, such as ERCP ± ES, need an experienced and skilled endoscopist to be successful.[26] Even after ERCP, ES is not always possible, and when ES is successful the duct is not always cleared of stones.[25,26]

Although useful, the endoscopic procedures are not without cost, morbidity, mortality, and significant lifestyle disruption. It has been seen that ERCP increases total cost to twice that of LCBDE.[26] For ERCP ± ES, the stone clearance rates are 65–75% after one session and increase to 85–92.5% after three sessions.[39] The success rates decrease in patients with altered anatomy, such as intra-diverticular papilla, abnormal localization of papilla, retropancreatic stenosis of bile duct, Billroth II bypass, and Mirizzi syndrome.[26,39]

ERCP ± ES has a morbidity of 7.6–13.5% and includes the risk of pancreatitis, bleeding, perforation, cholangitis, delayed stricture of sphincter, residual/recurrent stones, papillary stenosis, and mortality of 0.4–0.55%.[25,26]

Preoperative ERCP also causes bacterial contamination of CBD.[12,26] It has been seen that all recurrent stones after ES are bilirubinate type regardless of the type of initial stones, indicating a role of reflux with infection due to ablation of the sphincter.[12,25,26] Post-ES stricture of the sphincter with proximal residual dilatation of CBD also has been postulated to cause stasis of bile and recurrent stone formation.[26,39] Late papillary stenosis is observed between 10 and 33%, with recurrent stone formation and subsequent cholangitis.[9,26]

With advancing technology, laparoscopic biliary surgery has become safe, efficient, and cost-effective.[40] Randomized trials, comparing two-stage (pre- or postoperative ERCP/ES and laparoscopic cholecystectomy) versus single stage (laparoscopic cholecystectomy with LCBDE) reported similar success rates.[30,31,39] Laparoscopic CBD exploration was associated with successful stone clearance rates ranging from 75 to 95%, morbidity of around 10%, and mortality of approximately 1.5%.[30,32,40] Patients treated by LCBDE had a significantly shorter hospital stay and lower hospital cost compared with those who underwent a two-stage procedure.[30,31,39] Cuschieri et al. concluded that laparoscopic treatment was preferable for ASA II and ASA III patients, whereas ERCP/ES was indicated for high-risk patients.[31]

The morbidity rate after ES followed by LC ranged from 3 to 16% (mean 13%), whereas after laparoscopy it ranged from 7 to 19% (mean 8%). The mortality rate after ES ± LC ranged from 0 to 6% (mean 2%) and was twice higher the rate after laparoscopy, which was 1%.[12,30,39]

Current scenario

Stones Diagnosed Preoperatively

The general trend of management of preoperatively diagnosed CBD stones has been by ERCP with stone extraction with stenting if indicated, followed by laparoscopic cholecystectomy. However single stage LCBDE is emerging as a primary and cost effective treatment modality with less morbidity.[30,31,39]

In elderly and unfit patients, ERCP and stone extraction from the CBD is the initial and probably the definitive treatment. It is also the initial treatment in patients presenting with jaundice, cholangitis or severe pancreatitis. Laparoscopic cholecystectomy is undertaken once the condition of the patient has improved. Biliary stenting is advocated for patients with large dilated CBD, multiple impacted stones or stones not completely removed by ERCP.[12]

For patients who are fit for surgery, the choice is between single stage operative exploration of CBD or a sequential approach i.e. preoperative or postoperative ERCP with ES along with laparoscopic cholecystectomy. ERCP has a morbidity rate of 5 to 9.8 % and a mortality rate of 0.3 to 2.3 %, mostly due to post procedural acute pancreatitis, duodenal perforation and bleeding.[31] Moreover it causes injury to the sphincter of Oddi which should be avoided in patients younger than 60 years.[26,32,36]

Recent studies indicate that one-stage management of CBD stones with LCBDE has less morbidity and mortality and is cost effective with a short hospital stay.[26,39] It treats both gallstones and CBD stones in single stage compared with sequential procedures, and can also be performed as a day care procedure.[40] LCBDE also preserves the function of sphincter of Oddi and hence prevents reflux-related complications, such as cholangitis and recurrent stones associated with sphincter damage.[26,32,36]

Performing ERCP along with LC implies organizational problems concerning the availability of an endoscopist in the operating theatre whenever needed. Finally, performing ERCP after surgery would raise the dilemma of managing CBD stones whenever ERCP fails to retrieve them because a third procedure would then be needed.[36]

Reference centres for laparoscopic surgery currently propose treating both gallbladder and CBD stones during the same laparoscopic procedure.[30-32,36] No consensus has been achieved concerning the best approach (laparoscopic or endoscopic) because the laparoscopic management of CBD stones has not had a wide diffusion till now. In situations where there are difficulties in performing a combined laparoendoscopic procedure or the laparoscopic experience is limited, it is safer to perform an ERCP followed by cholecystectomy.[36]

A number of studies have reported about the mid-long-term results of laparoscopic CBD exploration, with excellent results reported up to 15 years post surgery.[27,41-44] These studies have also pointed out the advantage of the laparoscopic approach over the endoscopic approach in maintaining an intact sphincter of Oddi, thus obviating the drawbacks of bile reflux in the lower end of the surgery in the long term. This is especially more important in case of young patients, where the incidence of post procedural bacteriobilia and recurrent stones has been linked to loss of the function of sphincter and the accompanying reflux into the lower end of the CBD.[27,44]

Stones Discovered Intra operatively

The available options are; (a) total laparoscopic clearance, (b) combined laparoendoscopic treatment, (c) conversion to open CBD exploration, and (d) post cholecystectomy ERCP.

If the surgeon is experienced the most appropriate treatment would be a total laparoscopic approach. Several cohort studies have shown that two thirds of the stones detected by intraoperative cholangiography can be removed via the trans-cystic approach.[45] However this may not be true in Asian population where the CBDS are often large, multiple and densely impacted in the CBD. For patients in whom trans-cystic extraction of CBD stones fails, laparoscopic choledochotomy and stone extraction may be performed. However, this approach requires experience in laparoscopic suturing and a CBD of adequate diameter.

A Cochrane systematic review by Martin et al. concluded that a single-stage treatment of bile duct stones via the cystic duct approach was recommended for intra-operatively discovered CBD stones.[26] In patients where it is not possible to clear the duct by this approach, a delayed postoperative ES should be the preferred option in most centres.

The other alternative to immediate treatment of CBD stones discovered at surgery is delayed treatment. Surgeons can insert a biliary stent through the cystic duct into the CBD and through the sphincter of Oddi.[26] This procedure ensures access to the bile duct for postoperative ES.

Stones Discovered Postoperatively

These patients are best managed by endoscopic clearance, which is considered as the least morbid procedure. Failure rates of upto 10 % have been reported.[26,31] In these situations the treatment options are either laparoscopic or open exploration depending on the surgical expertise and resources at disposal.

LESS

Laparoendoscopic single-site (LESS) surgery has emerged as an alternative to conventional laparoscopic surgery with some proven benefits.[46] Many clinical applications of LESS surgeries have been reported in the fields of gynaecology, urology, and general surgery. Although laparoscopic CBD exploration has a high rate of stone clearance rate and low morbidity and mortality, this technique requires the acquisition of suturing and knot tying skills.[46] Suturing and ligation are more difficult in LESS surgery, compared to conventional laparoscopic surgery due to the angle limitations.

Robotic

Recent developments in laparoscopic CBD exploration have focused mainly on implementation of robotically assisted surgery and new imaging methods.[47] Since FDA approval of the da Vinci robotic system (Intuitive Surgical, Sunnyvale, CA, USA) for general surgical procedures, several reports have addressed their application for biliary surgery. Most surgeons gain their first clinical experience with surgical robots when performing cholecystectomies. The da Vinci system currently is the most widely used robotic system.

Conclusion

The best treatment for choledocholithiasis is the one that is simple, reliable, readily available, and cost-effective for most patients. With advances in technology and an increasing experience in laparoscopic techniques making LCBDE feasible and safe, this has emerged as the favourable choice in the hands of experienced laparoscopic surgeon. The benefit of avoiding a preoperative ERCP, in an otherwise healthy patient with choledocholithiasis, is that it excludes the hazards associated with ERCP and keeps the ampulla anatomically intact. Moreover, the benefits of minimally invasive surgery can be extended to the subset of patients with large and/or multiple CBDS which are otherwise unfit for ERCP and ES and have to undergo open procedures for stone removal.

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Surgical Procedures for Gall Bladder Cancer

Vinay K. Kapoor

Staging laparoscopy

GBC is a biologically aggressive cancer; in addition to the usual lymphatic and vascular routes, it spreads by peritoneal dissemination also resulting in small surface deposits on the peritoneum (both parietal and visceral) and omentum which cannot be detected on US, CT, MRI or even PET. They are, however, easily visualized on laparoscopy and can be biopsied to confirm metastatic disease. Presence of peritoneal dissemination in GBC contraindicates laparotomy for resection as prognosis is very poor. Staging laparoscopy must be done in all patients with GBC thought to have possibly resectable disease on CT (including those who are PET negative) – detection of peritoneal dissemination on laparoscopy will avoid an unnecessary laparotomy. NCCN guidelines now recommend strong consideration of staging laparoscopy.

Distant LN biopsy

Even if an enlarged distant (celiac, superior mesenteric or aorto-caval) LN was not seen on preoperative CT, the first step at laparotomy (after a negative staging laparoscopy) should be to look for an enlarged distant LN at these sites – if present, it should be removed and subjected to a frozen section histopathology or imprint (touch) cytology – if positive, it indicates metastatic disease with poor prognosis and contraindicates resection. Distant LN biopsy can be performed laparoscopically also. Extended retroperitoneal lymphadenectomy including distant LNs has been described but not practiced by most groups.

Simple cholecystectomy

Simple cholecystectomy, wherein the plane of dissection is between the GB wall and the cystic plate (which is left intact), is adequate for mucosal (T1a) GBC because these lesions are not associated with LN spread; this can be performed laparoscopically also. The clinical problem, however, is definitive preoperative diagnosis and staging of T1a GBC which can be done by EUS alone. T1a GBC is, therefore, hardly ever a preoperative diagnosis and simple cholecystectomy will hardly ever be performed for an obvious GBC. The clinical application of this knowledge is when dealing with incidental GBC. If it was T1a disease AND if the cystic duct margin was negative AND if the cystic LN was negative, simple cholecystectomy alone will be enough and no more intervention (in the form of completion extended cholecystectomy CEC) is required.

Extended cholecystectomy (EC)

The terms extended and radical cholecystectomy have been used as synonyms to describe the same/ similar surgical procedures. We, however, prefer to use the term EC, which defines the extent of the surgical procedure. We do not recommend the term radical cholecystectomy for describing the surgical procedure for GBC because the term radical defines the oncological adequacy of the surgical procedure based on the result of histological examination of the specimen i.e. R0 resection. Radicality of a surgical procedure depends both on the stage of the disease and the extent of the surgical procedure. Thus, while even simple cholecystectomy (with no liver resection and no LN dissection) will be radical for a mucosal (T1aN0) GBC, even hepato-ligamento-pancreatico duodenectomy (HLPD) may not be radical for locally advanced GBC infiltrating liver, HDL (hepatic artery, portal vein, common bile duct CBD) and pancreas.

EC includes en bloc

- Removal of gall bladder
- Resection of a non-anatomical 2 cm wedge of liver around the GB bed in segments IVB and V. The distance of 2 cm is arbitrary – even 1 cm may be adequate or 3 cm may be taken. Liver parenchyma is divided but no major bilio-vascular pedicle is encountered except a branch of segment V pedicle and few terminal tributaries of right hepatic vein (RHV) and middle hepatic vein (MHV). Wedge resection can be performed with virtually no bleeding using high wattage cautery and Harmonic scalpel. Liver wedge can be taken around the GB fundus/ body only and not around the GB neck where the right main pedicle or right anterior pedicle lies only a few mm from the GB bed.
- Dissection of LNs in the hepato-duodenal ligament HDL (cystic, pericholedochal, porta hepatis, retroportal), those behind pancreas head and duodenal C (retropancreatic, retroduodenal) and

along the common hepatic artery (to the right of the celiac axis). Adequacy of LN dissection is reflected in the number of LNs identified in the specimen; a minimum of 6 LNs is considered adequate for GBC.

EC does NOT include a formal/ anatomical liver resection (as in IVB+V resection) and dissection of celiac (to the left of the celiac axis), superior mesenteric or aorto-caval LNs (which are considered distant LNs).

EC is curative for early GBC i.e. confined to GB wall (T1, T2) and LN spread limited to the HDL (N1). EC may be performed for GBC at fundus/ body with minimal liver infiltration (T3) but for GBC at neck with liver infiltration (T3), EC is not technically possible as the right main pedicle lies at a depth of a few mm in the GB bed at its neck and a 2 cm margin of liver will sacrifice the right main pedicle thus necessitating right hepatectomy (which in GBC translates into extended right hepatectomy because segment IV has to be removed).

EC has been performed laparoscopically also but we do not recommend it. If laparoscopic EC is to be performed, it should be done in patients with T1/T2 disease (no liver infiltration, no adjacent organ involvement) only – this should be confirmed by both CT and EUS and preferably laparoscopic US also.

Extended resections

Procedures more extensive than EC should be described as follows

Segment IVB + V resection
Segment IVB + V is an anatomical liver resection. Segment V branch of the right anterior pedicle is exposed and taken in the GB bed; vessels, usually 2-3, to segment IVB from the left hepatic artery (LHA) and left portal vein (LPV) are taken to the right of the base of the falciform ligament resulting in discoloration of segment IVB . Parenchyma is then divided when terminal tributaries of RHV and MHV are encountered. Technically, segment IVB +V resection is better than wedge as it is more controlled – bleeding is thus less. Segment IVB+V resection may be required to achieve R0 resection for GBC at fundus/ body with liver infiltration (T3) but is not suitable for GBC at neck with liver infiltration (T3) for reasons cited above.

Taj Mahal resection
Taj Mahal resection including segments IVB + V with total resection of the caudate lobe (segment I). This is a dome-shaped liver resection ending at the root of the middle hepatic vein (MHV) at the pinnacle of the dome. Taj Mahal resection requires multiple intra-hepatic biliary-enteric anastomoses. The resultant cut surface of the liver is large and thus allows a good view for intra-hepatic cholangio-jejunostomy.

Taj Mahal resection is suitable for GBC at neck involving CBD and biliary confluence but without involvement of right hepatic artery or portal vein. It has not become very popular, probably because of technical difficulties. It cannot be performed if RHA and/ or RPV are involved.

Central hepatectomy
Central hepatectomy (resection of segments IV, V and VIII) is an alternative to ERH which preserves the posterior sector (segments VI and VII) which is not involved in GBC. It can, however, be performed only if RHA/RPV is not involved. It has also not become very popular, again probably because of technical difficulties.

Extended right hepatectomy (ERH)
Right hepatectomy alone is never adequate for GBC; segment IV also has to be removed thus resulting in ERH. Modified ERH (removing only segment IVB and preserving segment IVA) has been described to preserve more liver parenchyma. ERH is required in GBC at neck with liver infiltration or if RHA/ RPV are involved.

Patients with locally advanced GBC often present with SOJ due to involvement of the CHD. Preoperative biliary drainage (PBD) has to be performed to bring serum bilirubin down to less than 3 mg before a major liver resection. This can be endoscopic if biliary ductal confluence is patent;

percutaneous transhepatic biliary drainage (PTBD) will be required if the biliary ductal confluence is involved.

If the functional liver remnant (FLR) is not adequate (<30% in patients without jaundice and <40% in patients with jaundice) hepatic failure may occur after a major liver resection and is responsible for mortality. FLR may be increased by portal vein embolisation (PVE) which causes atrophy – hypertrophy. For GBC, however, RPV as well as segment IV branch of LPV have to be embolised because ERH will be performed. IF RPV alone is embolised, segment IV (which will also have to be resected) will hypertrophy and cause technical difficulties. PBD will be required before PVE is planned. Staging laparoscopy should be performed before PVE and again before operation.

Adjacent organs

Colon
Right transverse colon is often involved in GBC (especially at fundus) and can safely be resected to achieve an R0 resection.

Pancreas
Involvement of pancreas (T3) may contraindicate resection unless pancreatico-duodenectomy is planned. PD when combined with EC will have the morbidity and mortality similar to PD itself but HPD i.e. major hepatectomy + pancreatico-duodenectomy is still associated with high mortality and does not offer survival advantage in GBC and is not recommended. Wedge resection of pancreas has been described for Involvement of (head of) pancreas.

Duodenum
Involvement of duodenum (T3) may contraindicate resection unless pancreatico-duodenectomy is planned. Segmental or sleeve resection of duodenum has been described (if pancreas is free).

CBD excision
Some groups recommend CBD excision as a routine to take care of occult periductal and perineural spread but in our opinion CBD excision is not a mandatory component of EC. It may be performed in some selected cases e.g.

a) GBC with surgical obstructive jaundice (SOJ) due to direct infiltration of CBD
b) Tumor in GB neck/ cystic duct which is close to the CBD so that a clear margin cannot be obtained if cystic duct margin is positive on frozen section.
c) Some surgeons advocate CBD excision in presence of extensive LN involvement in the HDL to ensure adequate LN dissection, but we do not agree as there are two other structures in the HDL viz. hepatic artery and portal vein which are not recommended to be excised to ensure adequate LN dissection in presence of extensive LN involvement. CBD may have to be excised, however, if the LNs are adherent to the CBD.
d) For papillary tumors in the GB which are more likely to be multi-centric or have intra-ductal spread to CBD.
e) GBC with choledochal cyst

Vessels
Involvement of major vessels in the HDL viz. hepatic artery and portal vein indicates poor prognosis and is a contraindication for resection in GBC. There are a few reports of resection and reconstruction of these vessels but does not improve survival in GBC unlike in cholangiocarcinoma, where it may be helpful.

Non-curative simple cholecystectomy
Some patients with disease confined to the GB i.e. T1, T2 disease may have distant LN spread or distant metastases. In such cases, while R0 resection is not possible, the GB can be removed without breaching any tumor plane thus resulting in an R2 resection. This, combined with adjuvant chemo-radio therapy, may result in better survival than nothing/ chemotherapy alone. While we do not recommend it as a procedure of choice, we suggest that it may be performed if the distant LN spread or metastasis is detected for the first time after laparotomy has been performed.

Completion extended cholecystectomy (CEC)
We had earlier proposed the term completion extended cholecystectomy (CEC) for the surgical procedure performed for the diagnosis of an incidental GBC diagnosed for the first time on histopathology in a GB removed for a presumed diagnosis of gall stone disease. CEC includes

resection of non anatomical 2 cm wedge of liver in GB bed in segments IVB and V and dissection of LNs as in EC.

At the time of reoperation, the cystic duct stump should be excised and sent for frozen section histological examination. If positive, CBD excision should be added to CEC.

Based on the reports of high incidence of port site metastases (which usually occur in the port of GB extraction but can very well occur in other ports also) after LC for GBC, we recommend full thickness (skin to peritoneum) excision of all 4 ports of LC as a part of CEC. The upper 2 ports (midclavicular and epigastic) can actually be included in the subcostal incision used for CEC.

CEC has been performed laparoscopically also but we do not recommend it and prefer open operation. Recent reports, however, indicate that port excision is a staging procedure only and may not improve survival.

Summary of surgical procedures for gall bladder cancer

Oncologically, the aim is to achieve R0 resection.

- For T1 or T2 lesions (irrespective of their location in GB fundus, body or neck), both 2 cm wedge and IVB+V are equally effective; for lesions in GB neck, CBD excision may have to added. For T3 (liver infiltration) lesion in GB fundus/body, IVB+V resection may be better as the 2 cm wedge may not be adequate. For T3 (liver infiltration) lesion in GB neck, a 2 cm margin would include the right main pedicle. But right hepatectomy alone is not enough for GBC; segment IV has to be resected in GBC (cf. cholangiocarcinoma); it, therefore, amounts to ERH.
- Major surgical procedures e.g. ERH and HPD should be performed in highly selected good risk patients; mortality however, still remains high and long term survivals are few.
- Involvement of CBD and lymph nodes indicate poor outcome. Patients with distant metastases, distant LN involvement and major vessel (HA and PV) involvement are not candidates for resection.

T1, T2 (GB fundus/ body)	EC
T1, T2 (GB neck)	EC+CBD excision
T3 liver (GB fundus/ body)	IVB+V
T3 liver (GB neck)	ERH, modified ERH, central hepatectomy
T3 colon	EC + segmental colonic resection
T3 duodenum	EC + sleeve/ segmental duodenal resection
T3 pancreas	EC + PD
T4 hepatic artery or portal vein	Unresectable
Distant LNS	Inoperable
Distant metastases	Inoperable

Suggested readings

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Peritoneal Carcinomatosis

Chandra Bhushan Singh

Introduction

Peritoneal carcinomatosis (PC) is also referred to as peritoneal surface malignancy (PSM). It is a common evolution of cancer of the gastrointestinal tract (48% of gastric cancer with serosal erosion)[1], and ovaries and has been traditionally regarded as a terminal disease with short median survival. During the last 20 years, a renewed interest in peritoneal surface malignancies has led to development of new multimodal loco-regional therapeutic approaches thanks to its favourable oncologic results, combining cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC). This new therapeutic protocol has significant, but acceptable, morbidity and mortality, and high cost. It requires comprehensive management plan and careful patient selection.[2]

Peritoneal membrane

The peritoneum is a complex 3-dimensional organ covering the abdominopelvic organs and the abdominal wall, and contains a potentially large space. The most elaborate description of the ultrastructure of the peritoneum in man was presented in 1941 by Baron.[3] The peritoneum consists of a monolayer of mesothelial cells supported by a basement membrane and 5 layers of connective tissue, which account for a total thickness of 90 micrometers. The connective-tissue layers include interstitial cells and a matrix of collagen, hyaluron, and proteoglycans. The cellular component consists of pericytes, parenchymal cells, and blood capillaries. This complex is often referred to as the peritoneal membrane, and the description is a working model derived from research on the peritoneum as a dialysis membrane. Contrary to intuitive thinking, the elimination of the mesothelial lining during peritonectomy procedures does not alter the pharmacokinetic properties of the peritoneum in the transport of chemotherapeutic agents from the peritoneal cavity to the plasma compartment.[4]

Primary neoplasms of peritoneal and sub-peritoneal origin occur much less frequently than metastatic peritoneal involvement from a known or occult primary tumor; however, they can also present like PC. They are often first detected at computed tomography (CT) and should be considered in the absence of a known or suspected organ-based malignancy.[5]

Seeding and growth of cancers on the peritoneum are determined by many unique and incompletely appreciated properties of peritoneal cavity. Many of these cancers remain localized to the peritoneum only, never metastasizing to other sites. One possible reason for this may be the obstruction of the afferent lymphatics on the undersurface of the diaphragm. The mucopolysaccharides produced by many of these neoplasia are probably viscous enough to obstruct these lymphatics, leading to the syndrome of pseudomyxoma peritonei. Many of the neoplasms taking residence on the peritoneum have extremely long cell-cycle times and are resistant to radiotherapy and many chemotherapeutic agents. However, much can be done for these patients - resection of primary cancers, omentectomies to reduce ascites formation, management of recurrent ascites, management of intestinal obstruction, nutritional care, and, hopefully, intraperitoneal chemotherapy.[6]

Almost 15% of patients with colorectal cancer and almost 40% of patients with stage I and II gastric cancer present with Peritoneal Carcinomatosis (PC) at abdominal exploration.10%-35% of recurrent colorectal cancer (CRC) and up to 50% of recurrent gastric cancer (GC) patients have their recurrences confined to the peritoneal cavity. Most of these patients ultimately die from complications of locoregional tumoral spread, which occurs mostly without demonstrable spread to other sites. This natural unfavorable evolution of recurrence is commonly observed in epithelial ovarian cancer (EOC) too, a condition always associated with Peritoneal Carcinomatosis (PC) and in which locoregional spread of tumor is the most common cause of death. Preoperative diagnosis of PC could be very difficult. Imaging techniques (mainly based upon computed tomography scan and magnetic resonance imaging), assist in diagnosing PC, in planning cytoreduction and also in preventing unwarranted laparotomy in patients with unresectable disease. However, they are limited in their ability to visualize localized PC, having low sensitivity for small volume disease. The gold standard in diagnosing PC continues to be the direct peritoneal visualization, either by laparotomy or laparoscopy. Combined aggressive cytoreductive surgery (CRS), intraperitoneal hyperthermic chemotherapy (HIPEC) and systemic chemotherapy achieves increasing locoregional drugs concentration with

limited systemic diffusion and consequentially less systemic toxicity and adverse effects. The hyperthermia enhances the efficacy and the penetration of many of the drugs employed.[7]

Pathology

Cancers that occur within the abdomen and pelvis will disseminate by three different routes: hematogenous metastases, lymphatic metastases, and through peritoneal spaces to surfaces within the abdomen and pelvis. In a substantial number of patients, surgical treatment failure is isolated to the resection site or to peritoneal surfaces. The leading cause of death and suffering in patients with these malignancies is progression of peritoneal surface disease.[8] Biological research has identified three pattern of peritoneal cancer spread: (1) random proximal distribution (RPD), in which early peritoneal implantation is due to the presence of adherence molecules on cancer cell surface, even when ascites is present; this is typical of moderate-grade and high-grade cancers, such as adenocarcinoma and carcinoid of the appendix, non-mucinous colorectal cancer, gastric cancer and serous ovarian cancer; (2) complete redistribution (CRD), in which there is no adhesion to the peritoneal surface close to the primary tumor, due to the low biologic aggressiveness of tumor cells; this distribution is typical of pseudomyxoma peritonei and diffuse malignant mesothelioma; and (3) widespread cancer distribution (WCD), in which there is presence of adherence molecules on the surface of cancer cells that produce a great amount of mucus, interfering with cell adherence.[7]

Peritoneal Mesothelioma

Malignant mesothelioma is an uncommon tumor arising from the serosal layer of pleura, peritoneum, pericardium and tunica vaginalis testis. Exposure to asbestos is the etiology for it. Diffuse malignant peritoneal mesothelioma accounts for 10% to 30% of all mesotheliomas. Despite the absence of randomized studies, which are obviously difficult in a rare disease, clinical results obtained with the combination of cytoreductive surgery (CRS) and HIPEC makes it the treatment of choice for peritoneal mesothelioma.[7] In historical series, standard therapy with palliative surgery and systemic chemotherapy is associated with a median survival of about one year, ranging from 9 to 15 months. With such a classical approach, the disease tends to remain within the abdominal cavity throughout its clinical course. An autopsy study demonstrated that 78% of patients had died because of complications directly related to locoregional progression. On the contrary, Yan *et al* [9] in a recent multi-institutional study examined 407 patients affected by peritoneal mesothelioma treated with CRS and HIPEC in 7 different surgical centers. CC0-CC1 rates was achieved in 46% of cases, lymph nodes metastases were found in 6% and distant metastases in 3% of the patients. After a mean follow up of 30 months, the median survival was 53 months. A multivariate analysis showed that independent prognostic factors are - the histological type of the mesothelioma, the level of cytoreduction achieved, lymph node metastases, and the possibility to perform HIPEC.

Primary Peritoneal Carcinoma

Primary peritoneal carcinoma (PPC), was described for the first time by Swerdlow. [10] Its pathogenesis has been controversial. Some Authors believe that PPC develops from a malignant transformation of embryonic germ cell nests[11], other from the celomic epithelium lining the abdominal cavity (peritoneum) and the ovaries (germinal epithelium), manifesting a common response to an oncogenic stimulus.[12] A multifocal origin have been suggested by Muto *et al* [13] with clonality studies, while other authors suggest an unifocal origin. Even if from an histological and a clinically point of view PPC is similar to advanced epithelial ovarian cancer, it diffusely involves the peritoneum by papillary carcinoma in the absence of an obvious primary site and grossly normal ovaries.[14] It accounts for 10% of all pelvic serous carcinomas. Most reported cases of PPC have been described in women, usually elderly; however rare cases have been reported in children and males. Histologically most reported PPC cases are primary peritoneal serous papillary carcinoma, while rarely are they are described as peritoneal mixed epithelial carcinoma and malignant mixed Mullerian tumor. The prognosis of PPC is poor, the median survival time ranging between 7 and 27.8 months; 5-year survival rates range from 0% to 26.5%[15]. PPC diagnosis cannot be easily made preoperatively, being typically made by exclusion after both operative assessment and pathological study. In fact if ovaries seem normal with widespread disease elsewhere in the abdomen, PPC may be considered as a diagnostic possibility. However, because surface involvement of the ovaries is present in approximately 96% of the cases, the distinction between extra ovarian primary peritoneal cancer and epithelial ovarian carcinoma may only be made after histological examination to evaluate the extent of ovarian invasion by tumor.[16] Once diagnosed, maximal cytoreduction becomes the primary goal of the procedure.

Pseudomyxoma Peritonei

Pseudomyxoma peritonei (PMP), a syndrome firstly described by Rokitansky in 1842, is an enigmatic, often fatal intra-abdominal disease characterized by gelatinous ascites and multifocal peritoneal epithelial implants secreting copious globules of extracellular mucin. This condition is almost always due to a perforated epithelial appendix cancer. Three pathologic variant of PMP are known: disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA), and peritoneal mucinous carcinomatosis with intermediate or discordant features. The natural history of this disease has been drastically changed by the introduction of CRS combined with HIPEC. An overall 10 years survival rate of 78.9% in patients affected by PMP and treated with CC0-CC1 CRS has been reported, while 10 year survival in patients with CC2-CC3 CRS is not reported.

Staging of Peritoneal Carcinomatosis

The first role of imaging is to rule out the presence of distant metastases in extraabdominal areas, which is an absolute contraindication to CRS and HIPEC. The lesions in peritoneal cavity can be detected and analysed directly through ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT. Ultrasonography is useful in detecting ascites, large abdominal masses, or liver metastases. CT gives valid topographic representation of the abdominal cavity and a precise definition of site, type, and extent of the pathologic process. The main findings for peritoneal carcinomatosis on CT scan are focal or diffuse thickening of peritoneal folds, appearing as sclerotic, jelly-like, reticular, reticulonodular, nodular plaques. According to such an appearance, it is possible to identify different types of peritoneal carcinomatosis, namely infiltrative, micronodular (miliary), and macronodular (nodous) forms, with some overlapping among them. Nodular or plaque lesions can show various levels of enhancement after intravenous injection of contrast media, or even a little attenuation, with cyst-like appearance. Sometimes it is possible to see calcification deposits inside the lesions. Mesenteric involvement is often of the sclerotic type, with thickening and retracted appearance of the single layers. In the greater omentum it is often possible to see reticular/micronodular, or a nodular aspect and/or large plaques (“omental cake”). Ascites is present in more than 70% of cases, free or entrapped. CT scan can help in the preoperative evaluation of the peritoneal cancer index (PCI),[17] and shows 88% sensitivity and 12% accuracy. Magnetic nuclear resonance shows no advantages when compared with CT in the evaluation of PCI and in the prediction of achievable cytoreduction index. 18F-FDGPET, if used alone, underestimates PC.[18]

Role of Staging Laparoscopy

Video-laparoscopy (VLS) is considered an excellent diagnostic procedure, but its wide application in peritoneal carcinomatosis has been discouraged. The objections to this technique being related to:

- Difficulty of trocar positioning in the presence of abdominal wall tumor masses or adhesions from previous surgery
- Skepticism about the reliability and efficacy of the procedure in the staging phase
- Fear of neoplastic contamination of the port sites, supported by the finding of 52% of recurrences for pseudomyxoma peritonei along the surgical scar[19]

Diagnostic imaging (CT and CT/PET) is still considered the first and mandatory diagnostic test for peritoneal carcinomatosis.

Surgical Technique of VLS

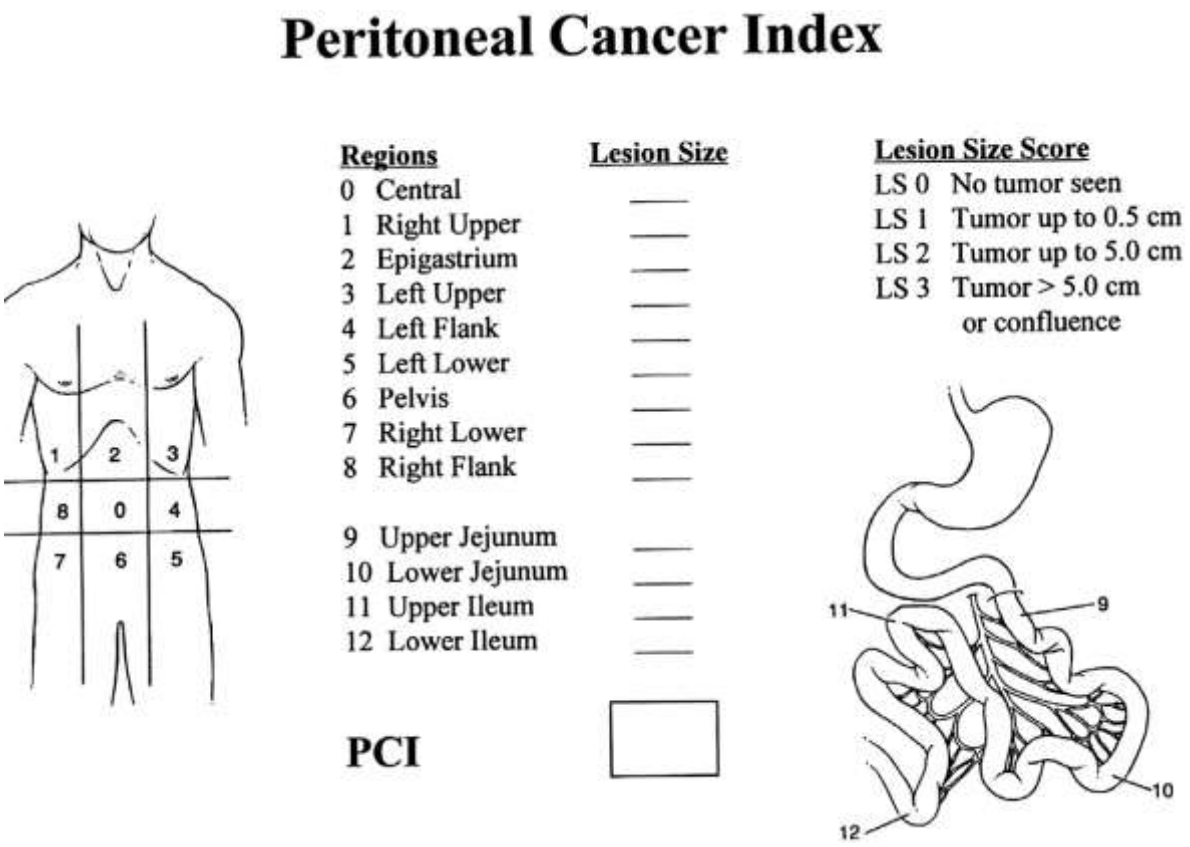
The Hasson trocar is introduced and the ascites completely sucked out of the peritoneal cavity, taking care not to contaminate the port sites. Considering the high incidence of adhesions both from previous surgery and from tumor masses infiltrating the midline, the choice is to avoid median or paraumbilical access(right or left flank or iliac fossa) on the mid-axillary line after carrying out clinical evaluation and ultrasound scan of the considered quadrants. This access allows for a better exposure of the small bowel and its mesentery even in presence of a large omental cake; it also offers the possibility of improving visualization by inserting a second trocar (5mm) beneath the first one or in the contralateral iliac fossa.A 30 degree scope is routinely used; division of adhesions should be kept to a minimum to avoid the risk of cutting through lesions and causing damage to abdominal organs, but should be enough for a complete evaluation of the PCI.[20]

Benefits of VLS

- Evaluation of the small-bowel mesentery (superficial lesions and retractions)
- Evaluation of all the sectors according to the PCI scoring system
- Evaluation of small-bowel lesions on the antimesenteric margin
- Evaluation of the omental bursa, pelvic cavity, diaphragm, and abdominal wall
- Possibility of peritoneal washing and biopsies for defining the histology of the primary tumor
- Predictive evaluation of the completeness of cytoreduction score (CC) index following peritonectomy

Locoregional Staging

Sugarbaker's classification for staging of PC is more useful for both prognosis and research, and is based on the PCI. The abdomen is divided into 9 sectors and the small bowel into 4 more parts; for each sector a score is assigned (Lesion Size score [LS]) related to the actual disease. The expected achievement of CC0 remains the main prognostic factor.[21]



Peritoneal cancer index[17]

Management

Investigations

CT features combined with the patient's relevant clinical and demographic data can help narrow the differential diagnosis for a peritoneum-based neoplasm in many cases. CT is useful for guiding biopsy for tissue diagnosis.

Clinical Assessment

Currently, there are four important clinical parameters of PC which are used to select patients who will benefit from treatment protocols: the invasive character of the malignancy, the preoperative computed tomography (CT) scan of abdomen and pelvis, the Peritoneal Cancer Index (PCI), and the completeness of cytoreduction score (CC).[8]

Extent of carcinomatosis and staging

The most important prognostic factor, whatever the origin of PC, is the completeness of cytoreduction (CC). The residual disease after cytoreductive surgery is classified using the CC score. CCR-0 indicates no visible residual tumor and CCR-1 indicates residual tumor nodules ≤ 2.5 mm. CCR-2 indicates residual tumor nodules between 2.5 mm and 2.5 cm. CCR-3 indicates a residual tumor >2.5 cm. HIPEC is indicated when carcinomatosis is amenable to effective cytoreductive surgery allowing a CC score ≤ 1. The probability of complete cytoreduction is correlated with the extent of PC. Thus, the extent of carcinomatosis represents one of the most important prognostic factors. [22]

Treatment

Patients are thoroughly evaluated to make sure that cancer has spread only to the peritoneal surfaces. If cancer has spread through the bloodstream to other sites such as the liver or lungs, or if there is extensive retroperitoneal lymph node involvement then patients should be treated with systematic chemotherapy.

Cytoreductive Surgery is a comprehensive surgical procedure that is used to remove tumors that have spread throughout the abdomen and pelvis and that are characterized mainly by the absence of spread through the bloodstream. Cytoreductive surgery includes a technique known as Peritonectomy Procedures which means that these tumors that are ON the peritoneal surface and not IN, can be stripped from the inner lining of the abdomen. During this process it is common to spill numerous cancer cells into the abdomen; therefore the second component of the treatment strategy (Hyperthermic Intraperitoneal Chemotherapy or HIPEC) is used to eliminate any floating cancer cells and to attack any residual microscopic disease.

Current indications for combined treatment using CRS and perioperative intraperitoneal chemotherapy[8]

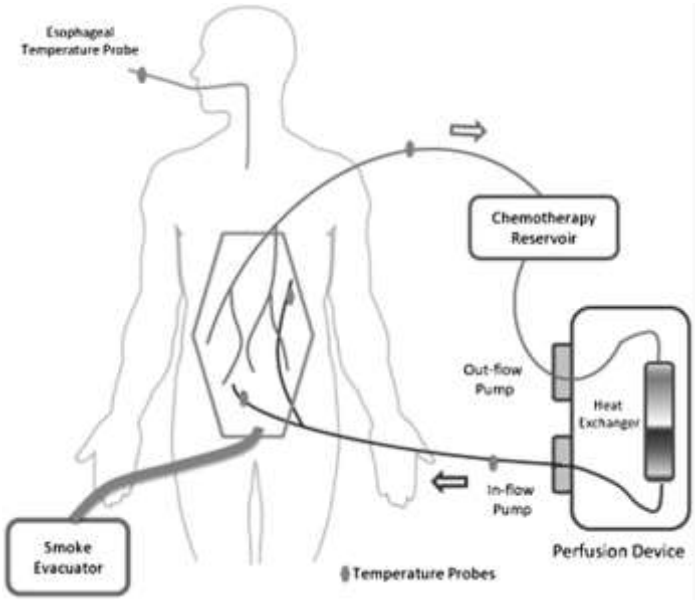
- Symptomatic malignant ascites
- Pseudomyxoma peritonei after complete cytoreduction
- Peritoneal mesothelioma after complete cytoreduction
- Primary colon or rectal cancer
- Perforated colon cancer
- Colon cancer with adjacent organ involvement
- Colon cancer with spread to the ovaries
- Tumor spill with resection of primary colon or rectal cancer
- Recurrent colon or rectal cancer with carcinomatosis
- Recurrent ovarian cancer with spread limited to peritoneal surfaces
- Primary gastric cancer after complete resection with limited peritoneal seeding
- Primary or recurrent abdominopelvic sarcoma
- Primary abdominopelvic sarcoma with equivocal margins of resection
- Primary abdominopelvic sarcoma with tumor spill during resection

Effect of Hyperthermia

Adding hyperthermia to protocols for perioperative cancer chemotherapy adds significantly to the logistic challenge of the procedure, and as such needs scientific validation. Adding hyperthermia to IP (intraperitoneal) chemotherapy increases the tumor response to cancer chemotherapy through several mechanisms. Firstly, heat alone has a direct antitumor effect. Mild hyperthermia above 41 degrees Celsius induces selective cytotoxicity of malignant cells by several mechanisms: impaired DNA repair, protein denaturation, and inhibition of oxidative metabolism in the microenvironment of malignant cells. This process leads to increased acidity, lysosomal activation, and increased apoptotic cell death.[23]Secondly, applying mild hyperthermia augments the cytotoxic effects of some chemotherapeutic agents. Synergy between heat and cancer chemotherapy drugs may arise from multiple events such as heat damage to adenosine triphosphate– binding cassette transporters (drug accumulation), intracellular drug-detoxification pathways, and repair mechanisms of drug-induced DNA adducts.[24]Such augmented effects are postulated for doxorubicin, platinum complexes, mitomycin C, melphalan, and docetaxel, irinotecan, and gemcitabine. Thirdly, hyperthermia may increase the penetration depth of the cancer chemotherapy solution into tissues and tumor nodules.

Heated intraperitoneal chemotherapy (HIPEC)

Unique aspects of HIPEC surgery include hemodynamic alterations owing to induced hyperthermia, as well as the potential for nephrotoxicity secondary to the use of chemotherapeutic agents. Appropriate management of intravenous fluid therapy is critical for maintaining optimal end-organ perfusion, and avoiding renal injury. Attention must also be paid to electrolyte balance, coagulation, and the potential need for transfusion. During the intraperitoneal infusion of heated chemotherapeutic agents, patients develop a hyperdynamic, vasodilated circulatory state that is characterized by steady increase in heart rate and cardiac output that reaches its maximum between 70 to 80 minutes of the 90-minute heated chemotherapy phase. As the body temperature decreases after completion of the heated therapy, the hyperdynamic state begins to normalize, but may remain above baseline for 10 minutes after the chemotherapeutic lavage is concluded.[25]When the closed abdomen technique is used, increased intra-abdominal pressure may decrease venous return, and further aggravate hemodynamic lability.There is gradual rise in core temperature. The temperature and urine output must be documented every 15 minutes and communicated to the surgeon and perfusionist. The surgeon or perfusionist should decrease the temperature of the perfusate when the core temperature approaches 39 degree celsius. A variety of acid-base and electrolyte disturbances like lactic acidosis, hyperglycemia, and hyponatremia can occur. In cytoreductive surgery combined with perioperative intraperitoneal chemotherapy (PIC), which may be complemented by systemic chemotherapy , PIC may be administered with hyperthermic intraperitoneal chemotherapy (HIPEC) during the course of cytoreductive surgery, in the first 4 or 5 days after surgery in normothermic conditions (EPIC), or as a combination of both.[26]HIPEC is delivered in the operating room (OR) after the cytoreductive surgical procedure is finalized if a complete cytoreduction has been achieved (CC-0/CC-1). There are two main methods for intraperitoneal administration of hyperthermic chemotherapy: open abdomen technique and closed abdomen technique. Over the years mixed methods (semiopen or semiclosed) have been reported. In open method four closed suction drains are placed through the abdominal wall and made watertight with a 3/0 monofilament purse-string suture at the skin. These drains remain in place for the postoperative period. An inflow line is placed over the abdominal wall into the peritoneal cavity and may be secured by a silk tie at the retractor frame. A smoke evacuator is placed under the plastic sheet to clear chemotherapy vapors or small droplets that may be liberated during the procedure. During the 30 to 90 minutes of perfusion, all the anatomic structures within the peritoneal cavity and the laparotomy incision are uniformly exposed to heat and chemotherapy by continuous manual stirring of the perfusate performed by the surgeon.. Sugarbaker[27]also reported the use of a closed acrylic device with a lid, mounted on top of the coliseum to provide perfusate containment while allowing manual access to the peritoneal cavity for manipulation..Tthere is no evidence to establish the superiority of one method over the others regarding patient outcomes, morbidity, or surgical staff safety.The instillate's temperature reaches 43 to 45 degree Celsius after passing through the heat exchanger. After minimum intraperitoneal temperature of 41.5 degree Celsius is achieved the drug is then added to the circuit and the timer for the perfusion is started.



Schematic representation of the circuit and elements used for the administration of HIPEC

Surgical Smoke Exposure

Cytoreductive surgery uses high-voltage electrosurgery for visceral dissection and resection and for the electroevaporation of tumor nodules. The amount of smoke generated during this procedure exceeds that created during a regular surgical operation (eg, for colorectal cancer).25 This fact added to the length of the operation (10–12 hours) may result in cumulative exposure. Contrary to the exposure to chemotherapy, surgical staff tends to underappreciate the risks of electrosurgical smoke and the need to use protective measures. Just by its physical effects, surgical smoke may produce headache, nausea, and eye and respiratory tract irritation to healthcare workers in the OR.[28] A smoke evacuator should be ready for use from the beginning of the operation.

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Are cancer metastases organ specific?

Durgatosh Pandey, Manjunath NML, Mahesh Sultania

Introduction

An attribute, which clearly distinguishes a malignant from benign cell, is invasion and metastasis. Metastasis of a cancer is defined as the spread of cancer cells from the organ of origin (birthplace) to other distant organs. The basic principle in the carcinogenesis and further spread of tumor is the change in the genetic makeup of an individual cell. The purpose of various molecular and genetic studies is therefore focused on delineating these secrets of nature. This has a great potential in discovering newer drugs or molecule, which can be used to curb the progress of cancer cell at various steps of cancer progression.

Although the field is rapidly progressing in the investigations related to cell proliferation, cell death, proto-oncogenes, tumor suppressor genes, genomic instability, and signal transduction pathways, progress in the field of metastasis in cancer as such is slow. The main reason is the technological constraints of humans in understanding the complex in-vivo processes with regards to metastasis. For better comprehension, the topic can be understood as the processes related to changes in the cancer cell, the organ of metastasis, and the host immunological responses (Box 1).

Box 1 – Principles of cancer metastasis

- Tumor cell
- The organ of metastasis
- Host immunological response

Historical background of cancer metastasis - Timeline

Before understanding the basic concepts of cancer metastasis, one should know the historical background of these principles. The persons and the institutions involved, the development of various technologies, experiments, and animal studies need to be comprehended. Dr Stephen Paget, an English surgeon gave an hypothesis for organ specific metastasis(1). Even though none of the genes or molecules were defined at that time, conclusions made by Dr Paget through his observations hold true even today. He gave the name seed and soil theory for his hypothesis. These conclusions were derived by the autopsy findings of more than 900 patients with different malignancies. The findings indicated that the outcome of metastasis was not due to chance (the prevailing viewpoint of that time), but that certain tumor cells (which he equated to the ‘seed’) have specific affinity for the milieu of certain organs (which he equated to the ‘soil’). He concluded that metastases formed only when the seed and soil were compatible.

Dr Paget gave a message, which is often repeated by every author involved in cancer research; “The best work in the pathology of cancer now is done by those who...are studying the nature of the seed. They are like scientific botanists, and he who turns over the records of cases of cancer is only a ploughman, but his observations of the properties of the soil might also be useful”.

Dr James Ewing in the year 1929 questioned Paget’s theory and proposed that organ specific metastasis is purely because of mechanical principles and not because of any interaction between cancer cell and organ of metastasis. The present understanding of the process of metastasis is the combination of these two theories. This is discussed in detail in the section of organ specific metastasis.

Cancer metastasis is organ specific – Evidence

To initiate further discussion, various metastatic sites of common malignancies are enlisted in the form of a table (Table 1). One can easily appreciate that a particular cancer metastasizes predominantly to a single organ. To understand the concepts behind this organ specificity in cancer metastasis, we have to grasp the nature’s principles and history of cancer metastasis. Here we have tried to present the recent and time-tested old concepts related to this topic.

Table 1 – Showing various organs of metastasis in different cancers

Cancer type	Most common site	Other common sites
Follicular thyroid cancer	Bones	
Colorectal cancer	Liver	Lung
Sarcomas	Lung	
Breast	Bone	Lung, Liver, Brain
Small cell lung cancer	Liver	Brain, Adrenals, Pancreas, Contralateral lung
Non Small cell lung cancer	Contralateral lung	Brain, Adrenals, Liver, Bone
Multiple myeloma	Flat bones	
Prostate cancer	Bone	
Ovarian Cancer	Peritoneal metastasis	
Uveal melanoma	Liver	

Note: Common sites may vary depending up on the referred series of patients. This is just to highlight the fact that cancer cell metastasis shows tissue tropism.

Why do they (Cancer cells) decide to leave their birthplace?

In the initial part, the growing tumor mass in any organ is avascular. By experiments, it is concluded that a tumor cannot grow beyond 1-1.5 mm in diameter, depending its nourishment on surrounding fluids(2,3). It starts deploying blood vessels to get its nourishment, which includes both oxygen supply and nutrition. This process is known as angiogenesis. This is the first step in cancer metastasis through which the cancer cells gain access to bloodstream. Apart from angiogenesis the cancer cells enable themselves to the process of metastasis through various predetermined and/or acquired mutations.

Cells without passport – Circulating tumor cells

Metastasis is a very inefficient process. Less than 0.01% of cancer cells released in to circulation can reach the organ of metastasis and establish as tumor deposits(4). The genetic events are incompletely understood. Figure 3 shows few genes and molecules in the various steps of cancer metastasis. These genes have been divided into initiating, progression and virulence genes (Box 2)

Box 2 – Genes and molecules related to metastasis

- Metastasis initiation genes
- Metastasis progression genes
- Metastasis virulence genes

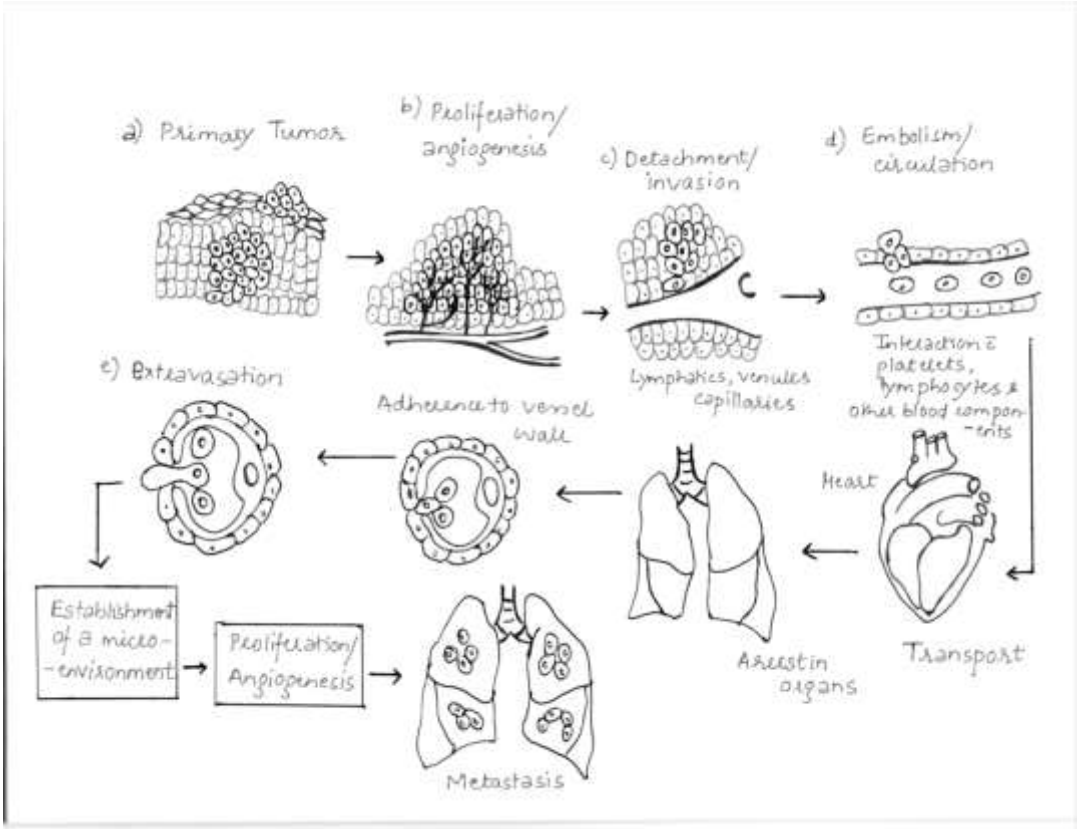
Tumor heterogeneity – Survival of the fittest

Cancer cells in a tumor mass can be compared to a cohort of students entering a medical school. They complete their under-graduation, post-graduation, PhD, specialization, Fellowships etc. Cancer cells similarly have different potentials and also gain certain functions due to ongoing mutations, as they have unstable genome. As we have understood already, the metastasis is a sequential process in which the cell has to have all necessary arrangements to complete that process. So in a tumor mass, among different cell types (clones), only few can complete all the steps and reach the metastatic organ and establish themselves as macro-metastasis. Also their genetic make-up decides their destiny; which organ they colonize and establish themselves.

Tumor heterogeneity also explains the fact, why certain tumors progress so fast and others show a long latency before spread. In certain types of tumors such as small cell lung cancer, the necessary alterations are present at the onset and relentless progress is set in within months. Thyroid cancers and some breast cancers show long latency, suggesting that the clonal genesis is slow, spanning over a period of years to decades.

Steps of cancer metastasis

Figure 1 illustrates various steps of cancer metastasis. Cells without the attributes of invasion and metastasis remain dormant for months to years (Preclinical stage). Progression towards metastasis is a continuous process. For better understanding, it has been divided in to sequential steps, which are overlapping. The sequence of events can be visualized as only one dimension of cancer metastasis.



The second dimension is the temporal kinetics of events and third is the organs in which these events take-place. This three dimensional conceptualization is necessary because we are looking at a process which is common to different heterogeneous types of malignancies.

Normal cells get transformed in to a cancer cell by acquiring uncontrolled growth potential. This transformation in a cell is brought about by various genetic alterations, which include proto-oncogenes, tumor suppressor genes; mismatch repair genes and many more. Next step is the infiltration of surrounding stroma. The cells secrete proteolytic enzymes that help in the invasion of basement membrane and stroma.

Once the tumor has established itself in the stromal tissue, it starts deploying blood vessels from the stromal cells. This process is known as the angiogenesis and genetic changes which flip the balance towards formation of new blood vessels is termed “Angiogenic switch”. Once they gain access to blood vessels, they penetrate the thin walled vessels and start their journey towards organ of metastasis as circulating tumor cells. The circulating tumor cells form tumor embolus by combining with platelets, leucocytes and fibroblasts. Further process of spread to distant organs is both mechanical and specific receptor mediated which will be elaborated further in next sections (Organ specific metastasis).

Extravasation of cancer cells from the blood vessels is either by trans-cellular or Para-cellular route(5). Tumor cell extravasation can also be achieved by tumor growth inside the vessel till the rupture of vessel wall and release of cells in to the organ of metastasis(6). Once the tumor cells settle-down in the organ, the process of angiogenesis is reinstated and whole process is repeated for further metastasis. One interesting phenomenon is the tumor self-seeding(7) in which the circulating tumor cells of virulent clone get deposited in the primary tumor as metastasis. This explains partly the reason for local recurrences after the surgical resection.

Cells settle down in most conducive environment – Seed and Soil hypothesis.

In the year 1889, Dr Stephen Paget came out with his “Seed and Soil” hypothesis to explain the organ specificity of cancer metastasis(1). Dr Paget observed the details of autopsy findings in 735 women, who died of metastatic breast cancer and he noticed that the metastasis was not random and followed a particular rule of organ specificity. He explained that the cancer metastasis is non random and is

organ specific in which the seed (Cancer cell) gets implanted in the suitable soil (Conducive organ microenvironment).

Various experiments in rodent models and clinical experiences in cancer patients have established that the tumor types tend to metastasize to specific organs, independent of the mechanical factors of vascular anatomy, rate of blood flow and the number of tumor cells delivered to each organ. Experiments with B16 melanoma cells derived from rodents, support Paget's 'seed and soil' hypothesis by showing preferential invasion and metastases in specific organs. When mouse melanoma cells were introduced into the circulation of syngeneic mice, tumor growths developed in the lungs and in fragments of pulmonary or ovarian tissue that were implanted intramuscularly. On the contrary, no metastases were found in the implanted renal tissue, or at the site of surgical trauma. This showed that the cancer metastasis is not, only determined by the specific cancer cell but also by the organ microenvironment(8).

Human experiments are impossible because of the ethical considerations, but the introduction of peritoneo-venous shunts for the palliation of ascites in women with progressive ovarian cancer has provided the opportunity to study some of the factors that affect metastatic spread in humans. The unique nature of ovarian cancer cells is their predominant trans-peritoneal spread. David Tarin and colleagues studied metastasis in ovarian cancer patients whose ascites were drained into the venous circulation. The procedure allowed the entry of viable cancer cells into the jugular vein. The autopsy findings from 15 patients substantiated the clinical observations that the shunts did not significantly increase the risk of metastasis to organs outside the peritoneal cavity. In fact, despite continuous entry of millions of tumor cells into the circulation, metastases to the lung, the first capillary bed encountered were rare(9). These results confirm the truth behind the seed and soil hypothesis. Similar animal experiments involving different cancer cells and organ of metastasis have shown the same findings(10).

Contrary to seed and soil hypothesis, the proponents of mechanical theory explained various examples of organ metastasis purely on mechanical grounds. The predominance of liver metastasis in GI malignancies, because of the peculiar venous drainage in to liver through portal circulation, bone metastasis (vertebral), from prostate cancer through venous plexuses, absence of cardiac metastasis because of the continuous movements and ovarian metastasis in fixed portions of peritoneal cavity are some of the examples to explain the mechanical theory. Both the theories are true and the present theory is the amalgamation of both the theories. So definitely organ metastasis is organ specific and both mechanical factors and genetic (seed and soil) concepts play a role in individual cancers.

Organ specific metastasis in common malignancies

Bone metastasis

Bone is the most common site for cancer metastasis. Both mechanical factors and chemokines are responsible for the predominance of bone metastasis. The fenestrated structure of bone marrow sinusoid capillaries is more permissive to cancer cell infiltration than the contiguous structure in other organs. The biochemical factors include acidic pH, high extracellular calcium content; provide microenvironment that is conducive to the growth of cancer cells(11). The chemokines and growth factors such as osteopontin, osteonectin and stromal derived factor – 1 play a role in hijacking the breast cancer cells(12,13). Various ligands and cancer cell receptors have been shown in table to exemplify their role in bone metastasis (Table 2).

Table 2: Showing various cancer specific factors involved in metastasis

Type of cancer	Organ of metastasis	Molecules involved	
		Seed (Cancer cell)	Soil (Organ)
Breast cancer	Bone	CXCR4, Parathyroid hormone related peptide (PTHrP)	CXCL12
Prostate cancer	Bone	Tetra saccharide sialyl Lewis X (sLe^X) antigen	E-Selectin
Cutaneous Melanoma	Lung	? Pro-inflammatory products	VEGFR-1 MMP-9
Colon cancer	Liver	Tetra saccharide sialyl Lewis x and a (sLe^X, sLe^a) antigen, EGFR	E-Selectin

Lung metastasis

The lung is the second most common site for the occurrence of metastasis. Carcinoma breast, sarcomas, bladder cancers, skin melanomas, renal cell carcinoma and head and neck cancers are common malignancies, which have predilection for lung metastasis. The dense vascular surface area of the lung makes it a particularly attractive micro- environment for supporting the outgrowth of metastases. Adult pulmonary vascular surface area spans to occupy as much as 100 square meters, which is significantly higher than that of any other organ. Various molecules involved in organ specific metastasis from melanoma and sarcomas are shown in Table 2.

Liver metastasis

The liver is a frequent site of metastasis for several tumors including colorectal, breast, lung, other GI cancers, cutaneous melanoma and neuroendocrine tumors. Choroid melanoma frequently metastasizes to the liver and this relationship cannot be satisfactorily explained by mechanical theory of cancer metastasis as postulated by Ewing. Major advance in the metastatic colon cancer with liver metastasis is the discovery of Epidermal growth factor receptor expression. The targeted therapy using Cetuximab has shown significant response rates and is being used in the management of this set of patients.

Brain metastasis

Nearly 50% of patients with metastatic lung cancer, >25% of patients with breast cancer, and 20% of patients with melanoma show brain metastasis. Blood brain barrier is major hurdle which cancer cells have to pass through. Recent investigations are beginning to provide insight into the cellular and molecular mechanisms that facilitate the recruitment and retention of tumor cells to the CNS. Genome-wide expression analysis on breast cancer cell brain metastatic variants identified the cyclooxygenase COX2, the EGFR ligand HB-EGF, and the a2, 6-sialyltranferase ST6GALNAC5, as critical mediators of extravasation through the blood-brain barrier(14).

Therapeutic targets

Angiogenic growth factors are the major targets of investigations pertaining to the organ microenvironment for cancer metastasis. Several therapeutic agents designed to inhibit VEGF-induced angiogenesis are now in clinical use including, monoclonal antibodies that block VEGF (bevacizumab), and small molecule inhibitors of the VEGFR-2 tyrosine kinase (e.g., sorafinib, sunitinib). The addition of bevacizumab to standard chemotherapy was shown to prolong progression-free survival and overall survival in patients with advanced non-small cell lung cancer (NSCLC)(15) and colon cancer. In colon cancer, the addition of bevacizumab to standard therapy increased the median duration of survival by 4.7 months(16).Various other targets are being investigated with the hope of obtaining therapeutic strategies against metastatic cancers.

Conclusion

Cancer cell metastasis is definitely organ specific. Both mechanical factors and molecular factors, which create cross talk between the cancer cell (seed) and organ of metastasis (Soil), play a role in the ultimate organ specificity of cancer metastasis. Even though various factors, molecules and genes have been delineated mainly in animal experiments and also to some extent in human cancer cells, therapeutic applications of them are few at present. Future trends should be turned towards better understanding of these targets to control the relentless progression of cancer cells and save many human lives suffering from metastatic cancer.

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Necrotizing Fasciitis

Deepak Ghuliani, Abhinav Agrahari

Necrotizing fascitis is a severe life threatening soft tissue infection characterized by a fulminant course and a high mortality. The aetiology is not fully understood, but most of the patients having necrotizing fascitis have some underlying pre-disposing factors which makes them vulnerable to infection. Early recognition, may be difficult as the disease is often clinically indistinguishable from other soft tissue infections early in the course of its evolution. A knowledge of all available tools is a key for an early accurate diagnosis. The laboratory risk indicator score can be useful for differentiating it from cases of cellulitis which can be managed by antimicrobial therapy alone. The mainstay of treatment is early complete surgical debridement with broad spectrum antibiotics, physiological support and a close intensive monitoring. Novel treatment strategies like hyperbaric Oxygen and Intravenous immunoglobulins have been proposed but their role still remains debatable.

What is necrotizing fasciitis?

Necrotizing fasciitis(NF) is a rapidly progressive soft tissue infection involving subcutaneous tissue upto the fascia that easily spreads along the fascial planes resulting in local soft tissue necrosis and life threatening severe sepsis. It has also been referred by several other names like flesh eating disease, flesh eating bacterial infection, synergistic necrotizing cellulitis, hospital gangrene, acute suppurative fasciitis, acute synergistic necrotizing fasciitis.

Historical perspective

A confederate army surgeon, Joseph Jones first described the disease during the civil war in 1871. By 1918 the cause of disease was identified as bacterial infection. Dr B.Wilson first coined the term Necrotizing fasciitis in 1952. Throughout the 19^{th} and 20^{th} century cases of NF occurred sporadically and was limited to the military hospitals during wars with few cases seen among the civilian population.The Center for Disease Control and Prevention (CDC) has reported that, worldwide, incidence of NF increased from the mid-1980s to early 1990s. Increase in the rate and severity of NF have been associated with increase in the prevalence of toxin-producing strains of *S. pyogenes* (M-1 and M-3 serotypes).

Aetiology and predisposing factors

Aetiology of necrotizing fasciitis is not completely understood and in several cases no identifiable cause has been found. Most of the patients have some predisposing factors which render them vulnerable to infection (Table 1). Bacterial entry usually occurs as a resultof some precipitating events like laceration, abrasion, cut, insect bite, contusion, burn, subcutaneous injection or operative incision that produces a breach in epidermis.(1)

Table 1. Predisposing factors for necrotizing fasciitis

Comorbid conditions

- Immunosuppression
- Diabetes
- Chronic disease
- Drugs, eg, steroids
- Malnutrition
- Age >60yrs
- Intravenous drug abuse
- PVD
- Renal failure
- Underlying malignancy
- Obesity

Aetiological factors

- Blunt or penetrating trauma
- Soft tissue infections
- Surgery
- IV drug use
- Childbirth
- Burns
- Muscle injuries

Pathophysiology

NF is a deep seated infection of the soft tissue that results in progressive destruction of fascia and fat with sparing of the skin initially.Deep fascia is the primary site of pathology in necrotizing fasciitis and the spread of infection along this plane occurs much earlier than the cutaneous changes.The cutaneous manifestations are secondary changes as a consequence of progressive ischemia and thus do not precisely reflect the extent of underlying the disease. Muscles usually are not affected. Organisms spread from the subcutaneous tissue, along the superficial and deep fascial planes facilitated by the production and release of bacterial enzymes, toxins and endogenous cytokines. This leads to activation of interleukins, TNF, interferons alpha, delta and gamma, which serves as a precursor molecule for capillary thrombosis, resulting in necrosis of the skin and subcutaneous tissue. The major pathological events include:

- spread of bacteria along fascial planes
- extensive destruction of tissues
- thrombosis of blood vessels
- ischemia and tissue necrosis
- damage to the superficial nerves producing localized anesthesia.

Microbiology

Most studies have revealed a polymicrobial nature of the disease with most cultures yielding a mixture of aerobes, anaerobes and facultative anaerobes. Infection with single organism is reported in about 15% of cases.(2) Overall the most common organism considered to be responsible is Streptococccus. Occasionally mycotic(fungal) species may also be responsible for necrotizing fasciitis.(Table 2)

Table 2 . Organisms identified in NF

Gram positive aerobes	**Gram negative aerobes**
Group A β hemolytic Streptococci	E. coli
Group B streptococci	Pseudomonas spp
Enterococci	Proteus spp
Coagulase negative staphylococci	Serratiaspp
Staphylococcus aureus	**Fungi**
Bacillus spp	Zygomycetes
Anaerobes	Aspergillus
Bacteroidesspp	Candida
Clostridium spp	**Others**
Peptostreptococcusspp	Vibriospp

Depending on the microbiological profile, NF can be divided into three groups:

Type I: (polymicrobial) 80% of cases of NF belong to this group. The infections are polymicrobial and synergism among bacteria results in a fulminant infection. The bacteriology includes a multitude of aerobes, anaerobes and facultative anaerobes.

Type II: (Monomicrobial) constitute around 20% cases of NF. The causative organism is mostly a gram +ve organism, most commonly Group A Streptococcus(GAS) alone or along with Staphylococcusaureus. In contrast to Type I, it canaffect any age group.

Type III: (Salt water NF) a variant of TypeI, it's a monobacterial gram –ve infection, most commonly by Vibriospp, where minor skin wound gets contaminated with Vibrio spp. 25% of cases occur due to wound contamination with sea water.(3) Despite an aggressive therapy mortality rates as high as 25% may be seen with this type.

Type IV: It occurs due to fungal infections after traumatic wounds or burns. Species like Aspergillus, Zygomycetes and Candida have been isolated.

Clinical features

NF may involve any part of the body but extremities, perineum and truncalareas get more commonly involved. NF does not have any predilection for age but occurs slightly more commonly in males. In the early stages (Stage 1 NF), NF presents only with pain , erythema, induration and tenderness and may be clinically indistinguishable from other soft tissue infections like cellulitis, erysipelas and impetigo.(4)

Stage 2 NF signals the onset of critical skin ishaemia with the formation of blisters and bullae. As the infection progresses the skin becomes increasingly tense ,erythematous with indistinct margins and the colour of skin changes sequentially from red purple to dusky blue with formation of bullae. On palpation crepitus may be palpated in the affected area. Blisters are formed by ischemia induced necrolysis as the perforators coursing through the fascia to supply the skin get progressively thrombosed by invading vessels. Cellulitis and erysipelas are rarely associated with the presence of blisters and bullae.

The onset of tissue necrosis signals the late stage(Stage 3) NF. Haemorrhagic bullae , skin anaesthesia and overt skin gangrene are changes characterstically seen in late stage NF.(4) Skin changes are usually heterogeneous and the clinical stage is decided by the skin area with most advanced skin changes.

Although early necrotizing fasciitis may be clinically indistinguishable from other soft tissue infections certain cutaneous features may be useful diagnostic clues. Unlike more superficial soft tissue infections margins of tissue involvement in NF are poorly defined, indistinct with the tenderness extending over the apparently normal skin. The pain is severe over the affected site and intense pain out of proportion to the physical findings is the hallmark cardinal manifestation.Lymphangitis is rarely seen in NF as the primary site of pathology lies in a deeper plane. (5) In cellulitis , where the pathology is seen around the lymphatic channels i.e. in the deep dermis and subcutaneous tissue lymphangitis is a more common finding.

Patients may also show signs of sepsis and shock like high fever, hypotension, prostration and multi organ failure. This is classically caused by superantigens elaborated by Group A Streptococcus and called as streptococcal shock syndrome. These patients may further pose diagnostic difficulties as they are confused, agitated and may even have a reduced level of consciousness.

Diagnosis

Early recognition of NF may be difficult as early evolving NF looks deceptively benign with lack of specific diagnostic clues.A high degree of suspicion, and low threshold to prompt surgical intervention should be the dictum. The diagnosis of NF is predominantly a clinical diagnosis and the information drawn from all investigations should be used in conjugation with the clinical diagnosis. A wide variety of diagnostic tools have been described to diagnose NF early and more accurately.

Laboratory findings

The laboratory findings commonly seen in NF includes leukocytosis, acidosis, altered renal function, hypoalbunemia and abnormal coagulation profile.(6) Labarotory risk indicator for necrotising fasciitis(LRNIEC) score described by Wong et al is one of the recently described diagnostic adjuncts for discriminating between NF and non necrotising soft tissue infections.(7,8) It is based on routinely available laboratory investigations for evaluating severe soft tissue infections. Six independent laboratory variables associated with NSTI are considered and each variable if present provides a specific number of points towards the final score.

LRINEC score

Value	LRINEC points
c-reative protein, mg/dL	
<150	0
>150	4
WBC counts, cells/cumm	
<15	0
15-25	1
>25	2
Haemoglobin levels, gm/dL	
>13.5	0
11-13.5	1
<11	2
Sodium level, mmol/L	
>135	0
<135	2
Creatinine level, mg/dL	
<1.6	0
>1.6	2
Glucose level, mg/dL	
<180	0
>180	1

The patients as per the risk of NSTI are categorised in three groups.(Table 3). The maximum score is 13 and a score of ≥6 raises the suspicion of NF and a score of ≥8 strongly supports the diagnosis.It was found that for intermediate and high risk cases(score>6) the score had a positive predictive value of 92% and negative predictive value of 96%. Thus it becomes a great tool for both confirming and discarding NF.(9)

Table 3. Patient categories within the LRINEC score according to the likelihood of NSTI

Risk category	LRINEC score, points	Probability of NSTI, %
Low	<5	<50
Intermediate	6-7	50-75
High	>8	>75

Imaging studies

Imaging modalities like plain X ray, USG, CT and MRI have also been used for establishing the diagnosis of NF. The prescence of subcutaneous air on plain Xray are seen in 57% of patients and is considered pathognomic for disease. But its absence does not exclude the diagnosis. CT and MRI prove useful in cases with equivocal signs and a doubtful diagnosis . Increased thickness of the fascial layers with or without enhancement on CT or MRI is suggestive of NF (10). The additional advantage of these studies is in identifying other causes of infection, particularly, deep abscesses if any.

Surgical diagnosis

The gold standard for detection of NF is tissue biopsy.(11) An incision over the site of maximal skin change is needed to assess the underlying tissue. Healthy subcutaneous fat and fascia indicates that further resection is not need and the morbidity to the patient is limited to a short scar. If the exploration reveals the presence of dusky gray necrotic subcutneous fat and fascia, lack of bleeding, thrombosed vessels, non contracting muscle, dish water coloured fluid(“dish water pus”) seeping from the wound and a positive finger test result the diagnosis of NF is confirmed. A positive finger test is characterised by lack of resistance to finger dissection in normally adherent tissues.

Tissue biopsies when sent for frozen section reveal classical histological findings like obliterative vasculitis of the subcutaneous vessels, acute inflammation and subcutaneous tissue necrosis .A correlation between histopathological finding and mortality in patients was recently demonstrated by Bableh et al. Based on haematoxylin and gram staining, the histopathology of NF was classified into three histological stages. Histological stages 1-3 were characterized by progressively increasing

bacterial proliferation and decreasing poly morphonuclear leukocytes infiltration. A mortality rate of 7.1%, 14.2% and 47% respectively were associated with histological stages 1-3.(12)

Excisional deep skin biopsy may be useful in diagnosing and identifying the causative organisms. Specimens are obtained from the spreading periphery of the necrotising infection or the deeper tissues revealed during surgical debridement.

Treatment

Once the diagnosis is established, treatment should be instituted without any delay. The treatment for NF follows the principles of treatment for any kind of surgical infection, i.e.

- source control
- antimicrobial therapy
- support
- monitoring

The extent of hemodynamic, respiratory, metabolic and renal compromise should be quickly evaluated. Early resuscitation with intravenous fluids (crystalloids or colloids) should be started along with the inotropes if needed.

NF is one of the excellent examples highlighting a very important role played by source control in management of surgical infection. Early and complete surgical debridement is the most important component of the treatment for NF. Several studies have shown the effect of early complete debridement on the final outcome in these patients. Mortality rates are consistently and significantly found to be lower in cases undergoing early, aggressive and complete debridement. (13) A generous incision is made and the macroscopic features of the lesion are used to decide the extent of debridement. Incision should be made to the deep fascia with excision of all non-viable tissue, including the fascia, drainage of all abscesses, and extensive fasciotomy. Healthy, viable, bleeding tissue at the edges of excision site should be the end point of debridement. To ensure that infectious process has not extended, a repeat surgical exploration 24-48hrs later, becomes essential. After the initial debridement, patient should be preferably managed in an intensive care unit which allows to provide a good physiological support along with close monitoring of the patient. Dictated by the state of the wound, repeated debridements should be done at intervals of 12 -48 hrs until no further necrotic or infected tissue is seen.

Reconstructive surgery should be planned once the paient is stabilized and infection is fully eradicated. Sterile dressings with alginate or hydrogel are used for wound coverage during the interim. Skin cover can be provided either with secondary skin suturing, split skin grafting or tissue transfer.

Negative pressure wound therapy is the vacuum assisted closure of wound. It improves healing and helps in reducing the size of larger defects that would have been difficult to manage with simply on their own.

Other forms of surgery which may be necessary include amputations for necrotizing infections of the extremities and a defeuntioning colostomy for perineal wounds to prevent continous faecal contamination.

Antimicrobial therapy

Antibiotics are an important adjunct to source control in NF. Broad spectrum anti-microbial therapy covering gram +ve, -ve, and anaerobic organisms should be instituted early with a special consideration for Group A Streptococcus and clostridial species. Recommended regimens include single agents like meropenam, imipenam, ertapenum and piperacillin-tazobactum, but maybe changed according to sensitivity. The commonly used multi agent regime includes a high does penicillin, clindamycin, and a fluoroquinolone or an aminoglycoside for gram –ve coverage. Antibiotics are continued till no further debridements are required and clinical status is improved.

Several novel therapies have been proposed in the management of patients with NF, but their role still remains controversial. One of the modalities reported for improving the outcome of this condition is hyperbaric oxygen(HBO). It is a type of medical treatment which involves intermittent inhalation of

100% O2 under pressures exceeding the atmospheric pressure. Hyperbaric oxygen creates a superoxygenated zone which forms a barrier against the spread of O2. This explains the observation by several study groups that HBO reduces the number of debridements required for wound control and also the mortality associated with the disease.

The absolute contraindications of HBO include chemotherapy with cisplatin and adriamycin, and untreated pneumothorax. Poorly controlled asthma, pregnancy, bone cysts, active neoplastic process and lung bullae, are the relative contraindications. The common side effects include ear pain due to inability to equalize middle ear pressure, sinus discomfort, convulsions and pulmonary edema due to O2 toxicity.(14)

Intravenous immune globulin has also been proposed in the treatment of NF, especially when associated with GrpA Streptococcal (GAS) infection. As per the Canadian experience, the use of IVIG looks reasonable in patients with Streptococcal toxic shock syndrome due to GAS infection and those with a higher mortality risk due to advanced age, hypotension and bacteremia .

Complications

- Septic shock
- Cardiovascular collapse
- Renal failure
- Scarring with cosmetic deformity
- Limb loss
- Toxic shock syndrome

Prognosis and outcome

NF is a life threatening condition with a high associated morbidity and mortality. Jones, who first described NF, reported a mortality rate of 46% and a recent pooled analysis estimated it to be around 34%. More recent studies have reported the mortality rates in the range of 16-24%, a rate lower than the rate at the time of first description of the disease, but still accounts for high mortality rates associated with NF.(9)

The outcome of the disease also depends upon the region involved; with the involvement of limbs having a lower mortality (22%) as compared to the truncal (44%) and perineal (28%) involvement. (15,16)The factors responsible for a higher mortality include late or incomplete debridement, age >60yrs, females, presence of hypotension, acidosis, bacteremia, renal failure, hyponatremia, PVD and a area involved more than $250cm^{3.}$ (17)

Fournier's gangrene

It is the NF of the perineum and genital area which may extend upto the abdominal wall. It is a TypeI NF (polymicrobial) first described by a French dermatologist Jean Alfred Fournier in 1883. Although initially described as an idiopathic gangrene of the genitalia, an identifiable cause may be found in 95% of cases. The necrotizing process usually begins from a infiltrative focus in anorectum, urogenital tract or the skin of the genitalia. It occurs more commonly in middle aged men (50-60yrs) and to a lesser extent in women and children. The aerobes and anerobes act synergistically to produce collgenase, heparinase, hyaluronidases, streptokinases and streptodornase, which causes rapid: digestion of fascial barriers, tissue destruction and necrosis.

Clinical features: In the prodromal phase of FG, genital discomfort and pruritis are the most common presenting complaints. This is followed by scrotal swelling, pain, erythema, induration and fever, which ultimately result in foul smelling necrosis.

Fournier's Gangrene Severity Index (FGSI): Laon et al developed the FGSI for prognostication and predicting mortality in FG. A score more than 9 is indication of mortality as high as 75%, whereas a score less than 8 has 75% survival chances.

Treatment: Aggressive, early and extensive surgical debridement is the mainstay of treatment. Broad spectrum antibiotics couveringgram+ve, -ve and aerobes and anaerobes, should be started. Care of the patient including intensive fluid resuscitation, nutrition, wound care should be initiated depending

upon the patient's condition. Urinary diversion in the form of supra pubic catheter or faecal diversion in the form of colostomy may be required in patients with extensive penile or perineal involvement.

Meleney's Gangrene

It is a rare variety of Type 1 of NF found in post operative patients at operative site; first described by Brunner and Meleney in 1926. It is a potentially fatal polymicrobial infection of the soft tissues by organisms which create a synergistic virulence and is also called as Postoperative Progresive Synergistic Gangrene. Usually develops as a complication of laparotomy wound, colostomy site or as a chronic ulcer in extremity. The inoculation of organism occurs from a surgical incision or drain site with the conditions affecting the immune response like diabetes being the risk factors. It is a slowly expanding lesion confined to the superficial fascia and appears as a painful erythematous area which later ulcerates progressing to gangrene. It is characterized by spreading cellulitis followed by formation of central ulcerated areas covered with eschar and necrosis. As with other forms of NF, surgical debridement with antibiotic therapy is the cornerstone of management.

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Deep Vein Thrombosis

Nikhil Talwar

Deep vein thrombosis (DVT) is clotting of blood in a deep vein of an extremity (usually calf or thigh) or the pelvis. DVT is the primary cause of pulmonary embolism. DVT results from conditions that impair venous return, lead to endothelial injury or dysfunction, or cause hypercoagulability. DVT may be asymptomatic or cause pain and swelling in an extremity; pulmonary embolism is an immediate complication. Diagnosis is by history and physical examination and is confirmed by objective testing, typically with duplex ultrasonography. D-Dimer testing is used when DVT is suspected; a negative result helps to exclude DVT, whereas a positive result is nonspecific and requires additional testing to confirm DVT. Treatment is with anticoagulants. Prognosis is generally good with prompt, adequate treatment. Common long-term complications include venous insufficiency with or without the postphlebitic syndrome[1,2,9-12].

DVT occurs most commonly in the lower extremities or pelvis. It can also develop in deep veins of the upper extremities (4 to 13% of DVT cases).Lower extremity DVT is much more likely to cause pulmonary embolism (PE), possibly because of the higher clot burden. The superficial femoral and popliteal veins in the thighs and the posterior tibial and peroneal veins in the calves are most commonly affected. About 50% of patients with DVT have occult PE, and at least 30% of patients with PE have demonstrable DVT[1,2].

Etiopathogenesis

Many factors can contribute to DVT (Table 1). Cancer is a risk factor for DVT, particularly in elderly patients and in patients with recurrent thrombosis. The association is strongest for mucin-secreting endothelial cell tumors such as bowel or pancreatic cancers[2,3].

Table 1: Risk Factors for Venous Thrombosis

- Age > 60 yr
- Cancer
- Cigarette smoking (including passive smoking)
- Estrogenreceptor modulators (eg,tamoxifen, raloxifine)
- Heart failure
- Hypercoagulability disorders:
    - Protein C deficiency
    - Protein S deficiency
    - Antiphospholipid antibody syndrome
    - Antithrombin III deficiency
    - Factor V Leiden mutation (activated protein C resistance)
    - Hereditary fibrinolytic defects
    - Hyperhomocysteinemia
    - Increase in factor VIII
    - Increase in factor XI
    - Paroxysmal nocturnal hemoglobinuria
- Immobilization
- Indwelling venous catheters
- Limb trauma
- Myeloproliferative disease (hyperviscosity)
- Nephrotic syndrome
- Obesity
- Oral contraceptives or estrogen therapy
- Pregnancy and postpartum
- Prior venous thromboembolism
- Sickle cell anemia
- Surgery within the past 3 months
- Trauma

Pathophysiology

Three conditions, first described by Rudolf Virchow in 1862, contribute to VTE formation: stasis of blood flow, endothelial damage, and hypercoagulability. **Lower extremity DVT** most often results from stasis (e.g., in immobilized patients), endothelial injury or dysfunction (e.g., after leg fractures), or hypercoagulability[2]. **Upper extremity DVT** most often results from endothelial injury due to central venous catheters, pacemakers, or injection drug use. Upper extremity DVT occasionally occurs as part of superior vena cava (SVC) syndrome or results from a hypercoagulable state or subclavian vein compression at the thoracic outlet[4].

1. Stasis

Although stasis alone is not sufficient, it is the most important factor in the development of deep vein thrombosis (DVT). The main event in the formation of a venous thrombus is the generation of thrombin in areas of stasis. This leads to platelet aggregation and fibrin formation.

2. Endothelial Damage

The role of endothelial injury is debatable. It is neither a necessary nor a sufficient condition for thrombosis. With the exceptions of hip arthroplasty and central venous catheters, there is little evidence that gross or microscopic venous injury has a role in venous thrombogenesis.

3. Hypercoagulable States

Abnormalities of the blood include aberrations of the clotting and fibrinolytic systems. Stasis and injury alone are not sufficient to cause thrombosis experimentally in the absence of low levels of activated coagulation factors. Patients who present at an early age with spontaneous venous thrombosis, who have a strong family history of DVT, or who develop recurrent venous thromboembolisms are usually considered "prothrombotic" or "hypercoagulable." These conditions are listed in Table 1.

(a). Inherited Thrombotic Disorders

These disorders should be suspected when a patient gives a history of unexplained venous thrombosis for e.g. spontaneous venous thrombosis, especially in unusual sites such as the mesenteric or the cerebral veins, a family history of thrombotic problems, and recurrent thrombosis with no apparent precipitating factor. Arterial thrombosis is notably absent, except as complicating mesenteric venous thrombosis where venous thrombosis could lead to bowel necrosis. Heparinization is indicated until the dose of warfarin sodium is adjusted. Prophylactic anticoagulation should occur before any type of surgical procedure[5].

(i) Antithrombin-III Deficiency

The most important inhibitor of coagulation is antithrombin III. In addition to acting on thrombin, antithrombin III inactivates factors Xa, IXa, XIa, plasmin, kallikrein, and factor XIIa. Its deficiency, an autosomal-dominant inherited trait, has significant clinical impact in the form of thrombosis. Recurrent thrombosis occurs in approximately 60 percent of patients, and pulmonary embolism occurs in up to 40 percent.

It is found more often in patients with serum albumin levels less than 3.0 g/dL. Patients with antithrombin III deficiency present as a resistance to heparin. Typically, heparin is given and no increase in the partial thromboplastin time (PTT) is noted. In this setting, immediate anticoagulation can be achieved by providing substrate (fresh frozen plasma) in addition to heparin and then conversion to oral anticoagulants[5].

(ii) Protein C Deficiency

Protein C is a vitamin K–dependent inhibitor of the procoagulant system. It forms in the liver and causes its inhibitory action by inactivating factors V and VII. Its inhibitory action is greatly facilitated by protein S. It is transmitted as an autosomal dominant trait, and 90 percent of the cases are because of a mutation in factor V (factor V Leiden mutation). Since the levels of Protein C are affected by warfarin, anticoagulation therapy with warfarin is sufficient3,[5].

(iii) Protein S Deficiency

Protein S is a vitamin K–dependent protein that is produced by hepatocytes and megakaryocytes. Its primary role is to function as a cofactor in protein C's inhibitory actions on factors V and VII. Protein C deficiency occurs as an autosomal-dominant disorder, but protein S deficiency can occur in the heterozygous and homozygous forms; the homozygous form generates symptoms earlier in life[5].

(b) Acquired Hypercoagulable States

(i) Lupus Anticoagulant Factor (Anticardiolipin Syndrome)

Lupus anticoagulant factors are antibodies that interfere with the in vitro partial thromboplastin time (PTT) by prolonging phospholipid-dependent clotting factors and also interfere with heparin monitoring. The presence of these antibodies is associated with an increased risk of arterial and venous thrombosis. These patients normally do not require anticoagulation therapy. Patients undergoing major surgical procedures should receive prophylactic anticoagulation therapy and mechanical prophylaxis[5].

(ii) Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia is a form of consumptive platelet activation. It is idiosyncratic in that the effect of heparin is not dose- dependent, and very small quantities of heparin can elicit the syndrome. The mechanism is thought to be autoantibody formation directed toward heparin and platelet surface antigens. Platelets are then activated and the clot consumed[5]. Mild transient thrombocytopenia occurs 2 to 4 days after heparin exposure; it may occur earlier if the patient has been exposed to heparin in the past. A more severe syndrome includes marked severe hyper-thrombocytopenia 6 to 12 days after heparin exposure and is associated with thrombosis. Arterial thrombosis is common and includes aortic and lower extremity vascular bypass grafts, femoral arteries, coronary arteries, and cerebral arteries[5].

The diagnosis is based on clinical suspicion and elimination of other causes of thrombocytopenia. It is possible to perform platelet aggregation studies using donor platelets and the patient's serum, plasma, and in vitro heparin. Discontinuation of the heparin results in lower morbidity and mortality, especially if the syndrome is detected early[5].

Screening for hypercoagulability

Patients presenting with a thrombotic episode at a young age or those with previous events should be screened for hypercoagulability[5,6].
Routine screening should include measurements of prothrombin time, activated partial thromboplastin time, hematocrit level, white blood cell count, sedimentation rate, and platelet count[5-7]. Measurements of homocysteine levels, antiphospholipid antibodies, protein C and protein S, antithrombin III, activated protein C resistance, platelet aggregation, and mutant factor V should be done in high-risk patients. Screening is difficult once anticoagulation has begun. For instance, coumarin derivatives interfere with measurements of proteins C and S and the functional assay for activated protein C resistance, heparin reduces circulating levels of antithrombin III, and antiplatelet drugs may produce false negatives when testing for heparin-induced thrombocytopenia[5].

Clinical Manifestations

The site of venous obstruction determines the level at which swelling is observed clinically. Calf vein thrombosis is localized to one or more of the three major named veins below the knee. Calf tenderness is frequently present, but because the thrombi are rarely completely obstructive and the veins are paired, swelling is not a universal finding. Femoral vein thrombosis usually is associated with swelling of the foot and calf. Iliofemoral venous thrombosis represents the most extensive form of DVT and usually is associated with tenderness in the groin and swelling of the entire leg. Major venous thrombosis involving the deep venous system of the thigh and pelvis produces a characteristic presentation of pain and extensive pitting edema. The extremity may have bluish discoloration (phlegmasia cerulean dolens) or blanching (phlegmasia alba dolens, or “milk leg”). The latter usually occurs in association with pregnancy[1-5].

Complications

Common complications include, Chronic venous insufficiency, Postphlebitic syndrome, Pulmonary embolism[6].

In **phlegmasia cerulea dolens,** massive iliofemoral venous thrombosis causes near-total venous occlusion; the leg becomes ischemic, extremely painful, and cyanotic. Pathophysiology may involve complete stasis of venous and arterial blood flow in the lower extremity because venous return is occluded or massive edema cuts off arterial blood flow. Loss of sensory and motor function and venous gangrene are likely unless an aggressive approach is implemented to remove the thrombus and restore blood flow. This condition almost always occurs with advanced malignant disease[6].

In **phlegmasia alba dolens,** a rare complication of DVT during pregnancy, the leg turns milky white. Pathophysiology is unclear, but edema may increase soft tissue pressure beyond capillary perfusion pressures, resulting in tissue ischemia and wet gangrene[6].

Rarely, venous clots can become infected. Jugular vein suppurative thrombophlebitis **(Lemierre syndrome),** a bacterial (usually anaerobic) infection of the internal jugular vein and surrounding soft tissues, may follow tonsillopharyngitis and is often complicated by bacteremia and sepsis[6].

Symptoms and Signs

DVT may occur in ambulatory patients or as a complication of surgery or major medical illness. Among high-risk hospitalized patients, most deep vein thrombi occur in the small calf veins, are asymptomatic, and may not be detected[1,2].

Only 40 percent of patients with venous thrombosis have any clinical signs of the disorder. When present, symptoms and signs (eg, vague aching pain, tenderness along the distribution of the veins, edema, erythema) are nonspecific, vary in frequency and severity, and are similar in upper and lower

limbs. Dilated collateral superficial veins may become visible or palpable. Calf discomfort elicited by ankle dorsiflexion with the knee extended (Homans sign) occasionally occurs with distal leg DVT but is neither sensitive nor specific. Tenderness, swelling of the whole leg, > 3 cm difference in circumference between calves, pitting edema, and collateral superficial veins may be most specific; DVT is likely with a combination of ≥ 3 in the absence of another likely diagnosis (Table 2) [2].

Low-grade fever may be present; DVT may be the cause of fever without an obvious source, especially in postoperative patients. If PE occurs, symptoms may include shortness of breath and pleuritic chest pain[2].

Table 2: Probability of Deep Venous Thrombosis Based on Clinical Factors

Factors

- Tenderness along distribution of the veins in calf or thigh
- Swelling of entire leg
- Calf swelling (> 3 cm difference in circumference between calves, measured 10 cm below tibial tuberosity)
- Pitting edema greater in affected leg
- Dilated collateral superficial veins
- Cancer (including cases in which treatment was stopped within 6 months)
- Immobilization of lower extremity (eg, due to paralysis, paresis, casting, or recent long-distance travel)
- Surgery leading to immobility for > 3 days within the past 4 weeks

Probability

Probability equals the number of factors, subtracting 2 if another diagnosis is as likely as or more likely than DVT.

- High probability: ≥ 3 points
- Moderate probability: 1–2 points
- Low probability: ≤ 0 points

Diagnosis

Diagnosis is typically by ultrasonography with Doppler flow studies (duplex ultrasonography). The need for additional tests (eg, D-dimer testing) and their choice and sequence depend on pretest probability and sometimes ultrasonography results. No single testing protocol is best; one approach is described in Fig. 1.

Ultrasonography

Venous duplex ultrasonography has relegated other non-invasive tests, such as radioactive-labeled fibrinogen scans and all types of plethysmography, to historical interest. Accuracy rates above 90 percent have been consistently reported for venous duplex exams[7].

There are three essential phases to the venous duplex scan: (1) thrombus visualization, (2) vein compressibility, and (3) venous flow analysis. Accuracy is dependent on the examiner's skill. Thrombus may be difficult to visualize in its acute form, and the addition of color flow imaging facilitates the identification of non-occluding clots. Thrombus echogenicity increases with age of clot. Venous compressibility is determined by placing the probe directly over the vein and applying gentle pressure while observing under B-mode imaging. Veins filled with thrombus do not collapse with this maneuver. Persistent lack of a flow signal indicates total obstruction. A negative scan performed by a well-trained radiologist is sufficient to rule out a DVT of the lower extremity[2,7,8].

D-Dimer

D-Dimer is a byproduct of fibrinolysis; elevated levels suggest recent presence and lysis of thrombi. D-Dimer assays vary in sensitivity and specificity; however, most are sensitive and not specific. A highly sensitive test is enzyme-linked immunosorbent assay (ELISA), which has a sensitivity of about 95%[7,8].

If pretest probability of DVT is moderate or high**,** D-dimer testing can be done at the same time as duplex ultrasonography. A positive ultrasound result confirms the diagnosis regardless of the D-dimer level. If ultrasonography does not reveal evidence of DVT, a normal D-dimer level helps exclude

DVT[7]. Patients with an elevated D-dimer level should have repeat ultrasonography in a few days or additional imaging, such as venography, depending on clinical suspicion (Fig. 1).

Venography
The role of venography has been diminished by the advances in ultrasound technology. Nonetheless, the injection of contrast material for direct visualization of the venous system of the extremity remains the most accurate method of confirming the diagnosis of venous thrombosis and the extent of involvement. The main indication for its use in the diagnosis of an acute DVT is a non-definitive duplex scan. Potential false-positive examinations may result from external compression of a vein or washout of the contrast material from venous flow from collateral veins[4,7].

***Other testing*:** Noninvasive alternatives to contrast venography are being studied. They include MRI venography and direct MRI of thrombi using T1-weighted gradient-echo sequencing. MRI can provide simultaneous views of thrombi in deep veins and subsegmental pulmonary arteries (for diagnosis of PE). If symptoms and signs suggest PE, additional imaging (e.g.ventilation/perfusion [V/Q] scanning or CT pulmonary angiography) is required[4].

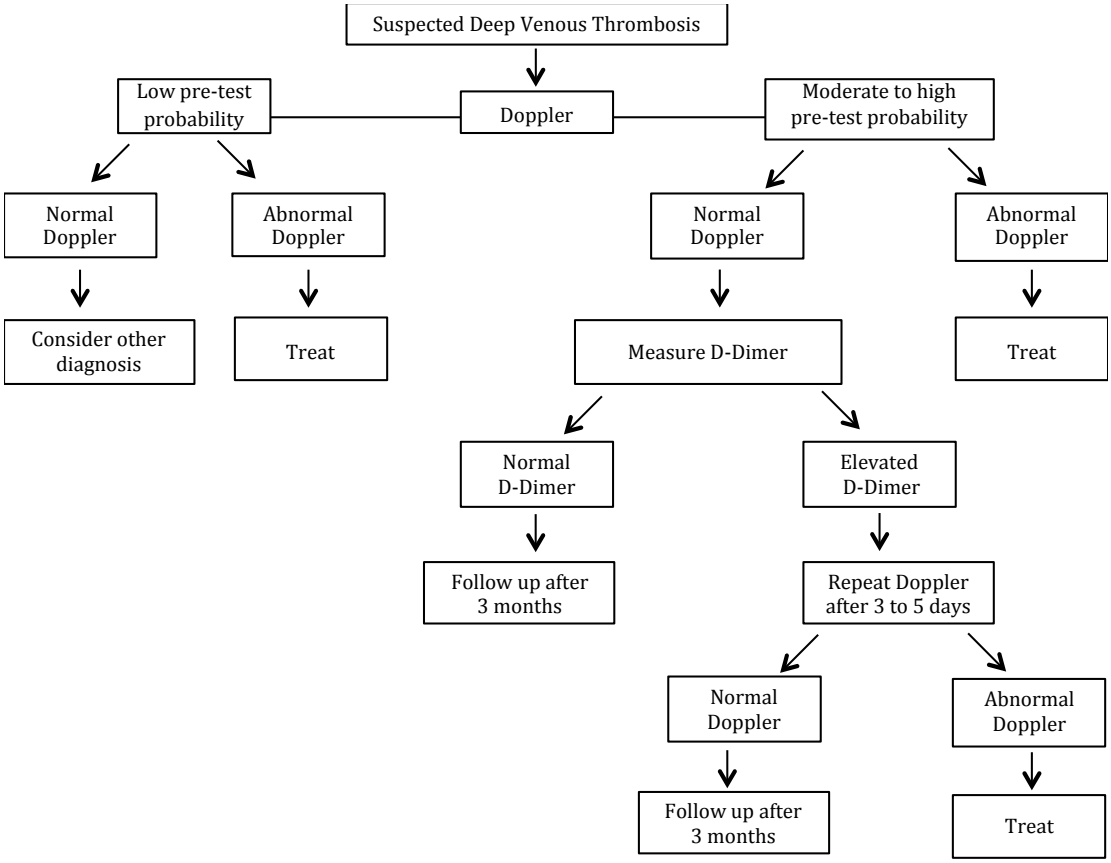

Fig. 1: Approach to testing for suspected deep venous thrombosis

Management

The foundation of therapy for DVT is adequate anticoagulation. All patients with DVT are given anticoagulants, initially an injectable heparin (or unfractionated or low molecular weight form) for a brief period, followed by longer term treatment with an oral drug (eg, warfarin) started within 24 to 48 h. Treatment is aimed primarily at PE prevention and secondarily at symptom relief and prevention of DVT recurrence, chronic venous insufficiency, and postphlebitic syndrome. Treatment of lower and upper extremity DVT is generally the same[1,2].

General supportive measures include pain control with analgesics, which may include short (3- to 5-day) courses of an NSAID. Extended treatment with NSAID's should be avoided because their antiplatelet effects may increase the risk of bleeding complications. In addition, elevation of legs

(supported by a pillow or other soft surface to avoid venous compression) is recommended during periods of inactivity[1,2].

Patients may be as physically active as they can tolerate; there is no evidence that early activity increases risk of clot dislodgement and PE and may help to reduce the risk of the postphlebitic syndrome.

Anticoagulants

The anticoagulants most often used are the following :

- Heparin (Unfractionated Heparin [UFH])
- Low molecular weight heparins (LMWHs) e.g enoxaparin, dalteparin, tinzaparin.
- Fondaparinux (a parenteral selective factor Xa inhibitor)
- Oral anticoagulants (coumarin derivatives): Warfarin, Acenocoumarol (Acitrom^{TM})
- Non-warfarin oral anticoagulants, also called direct oral anticoagulants(DOACs): factor Xa inhibitors (eg, rivaroxaban, apixaban), direct thrombin inhibitors (dabigatran) [10]

Heparin

Heparin is also called Unfractionated Heparin (UFH). Most commonly used preparations for DVT treatment has 1000 units/mL of solution. Unless there are specific contraindications, heparin should be administered in an initial dose of 80 units/kg intravenously. Heparin is an acid mucopolysaccharide that is given as a bolus and infusion (Fig. 2) to achieve full anticoagulation (activated PTT [aPTT] 1.5 to 2.5 times that of the reference range). Heparin neutralizes thrombin, inhibits thromboplastin, and reduces the platelet release reaction. It may be administered by continuous or intermittent intravenous doses (Fig. 2) regulated by wholeblood clotting time or APTT. Treatment is continued until full anticoagulationhas been achieved with oral anticoagulants[1,2,10].

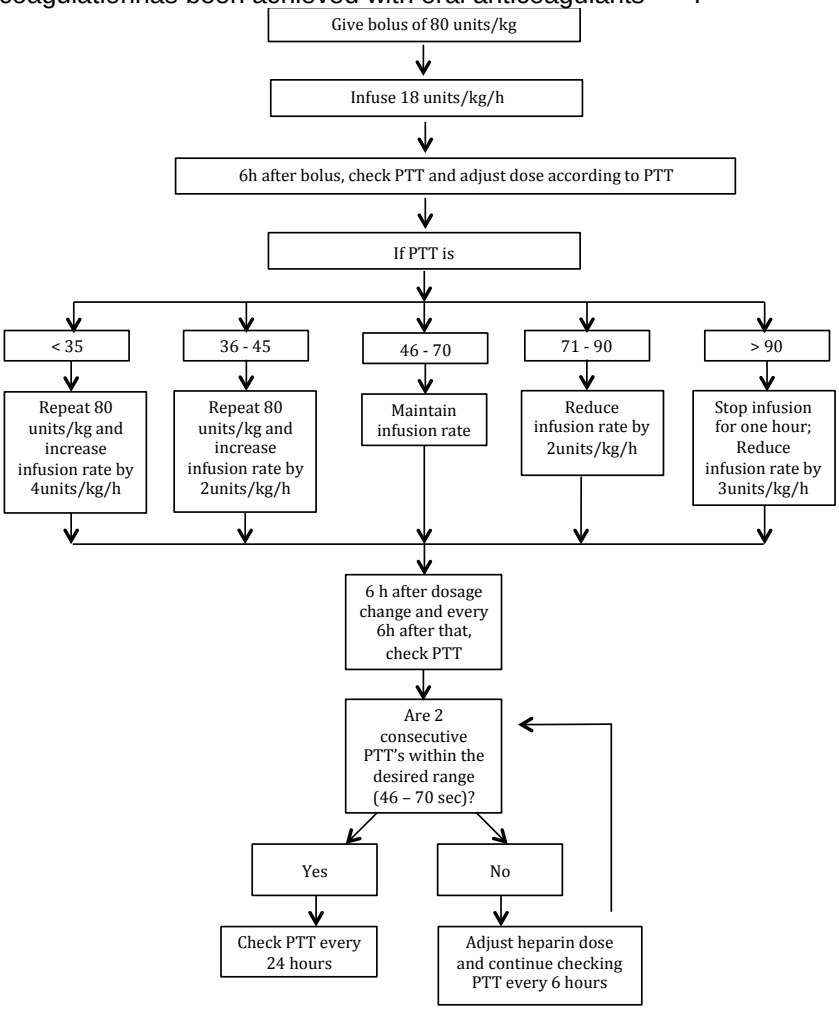

Fig. 2: Weight-based heparin dosing

Low Molecular Weight Heparins (LMWHs)
They are the initial treatment of choice because they can be given on an outpatient basis. LMWHs (e.g. enoxaparin, dalteparin, tinzaparin) are the treatment of choice because they can be given on an outpatient basis. LMWHs are as effective as Heparin for reducing DVT recurrence, thrombus extension, and risk of death due to PE. They have a similar mode of action as Heparin.

LMWHs are typically given subcutaneously in a standard weight-based dose (Table 3). Monitoring of PT/INR is not reliable because LMWHs do not significantly prolong the results of coagulation profile. Furthermore, they have a predictable dose response, and there is no clearrelationship between the anticoagulant effect of LMWH and bleeding. Treatment is continued until full anticoagulation is achieved with warfarin (typically about 5 days). LMWHs are an acceptable alternative to warfarin for some patients, although warfarin is likely to be the treatment of choice for most patients because of its low cost and oral route of administration[1,2].

Complications of heparins include bleeding, thrombocytopenia (less common with LMWHs), urticaria, and, rarely, thrombosis and anaphylaxis. Long-term use of UFH causes hypokalemia, liver enzyme elevations, and osteopenia. Rarely, UFH given subcutaneously causes skin necrosis. Inpatients and possibly outpatients should be screened for bleeding with serial CBCs and, where appropriate, testing for occult blood in stool[1,2,5].

Table 3: Some Low Molecular Weight Heparin (LMWH) Options in Thromboembolic Disease

LMWH	Treatment Dose	Prophylactic Dose
Dalteparin Brand names: Fragmin™	100 units/kg sc 12 hourly or 200 units/kg once/day	2500–5000 units once/day
Enoxaparin Brand names: Clexane™ Loparin™	1 mg/kg sc 12 hourly or 1.5 mg/kg sc once/day	• After abdominal surgery: 40 mg sc once/day • After hip or knee replacement surgery: 30 mg sc 12 hourly • For unstable angina or non-Q wave MI: 1 mg/kg sc 12 hourly • For other patients not undergoing surgery: 40 mg sc once/day
Tinzaparin	175 units/kg sc once/day(in patients with or without PE)	3500 units once/day

PE =pulmonary embolism

Bleeding due to over-heparinization can be stopped with Protamine. It is available as an IV solution of 10mg/mL .For more rapid reversal, 1 mg of protamine sulfate for every 100 units of heparin most recently administered is immediately effective. It is given as 1 mg in 20mL of normal saline infused slowly over 10 to 20 minutes. Monitor APTT after 15 minutes and then after 2 hours. Because Heparin given IV has a half-lifeof 30 to 60 min, protamine is not given to patients receiving Heparin (eg, if Heparin was given > 60 min beforehand) or is given at a dose based on the amount of estimated to be remaining in plasma, based on the half life of Heparin[1,2,9].

Protamine is strongly basic and combines with acidic heparin forming a stable complex and neutralizes the anticoagulant activity of the drug. During all infusions, patients should be observed for hypotension and a reaction similar to an anaphylactic reaction.

In case of LMWHs, the dose is 1 mg protamine for each milligram of LMWH. If a 2nd dose is required, it should be one half the first dose. However, the precise dose is undefined because protamine only partially neutralizes LMWH inactivation of factor Xa.

Patients on heparin undergoing surgery: The first step in managing these patients is discontinuation of heparin; this may be sufficient if the operation can be delayed for several hours. In an emergency situation, dosage of protamine as above is to be followed.

Fondaparinux
Fondaparinux (Arixtra™), a parenteral selective factor Xa inhibitor, may be used as an alternative to UFH or LMWH for the initial treatment of DVT or PE. It is given ina fixed dose of 7.5 mg sc once/day

(10 mg for patients > 100 kg, 5 mg forpatients < 50 kg). It has the advantage of fixed dosing and is less likely to cause thrombocytopenia[11].

Oral anticoagulants

Coumarin derivatives

Oral administration of anticoagulants is begun shortly after initiation of heparin therapy. Most commonly used oral anticoagulants are coumarin derivatives like warfarin and acenocoumarol (Acitrom™). There is a risk in giving coumarin derivatives to a patient who is not already anticoagulated with heparin. These coumarin derivatives block the synthesis of the vitamin K dependent clotting factors and inhibit vitamin K carboxylation of proteins C and S. A vitamin K antagonist potentially can create a hypercoagulable state before achieving its anticoagulant effect because the half-lives of proteins C and S are shorter than the half-lives of the other clotting factors. 5 to 10 mg can be started immediately with heparins because it takes about 5 days to achieve desired therapeutic effect. Heparin should be continued for the 4 to 5 days required to achieve full anticoagulation with coumarin derivatives. Therapeutic goal is an INR of 2.0 to 3.0. INR is monitored every 2 to four days till it reaches the therapeutic range (see Fig. 3); the dose is increased or decreased by 0.5 to 3 mg to maintain the INR within this range(Table 4). Patients taking should be informed of possible drug interactions[10].

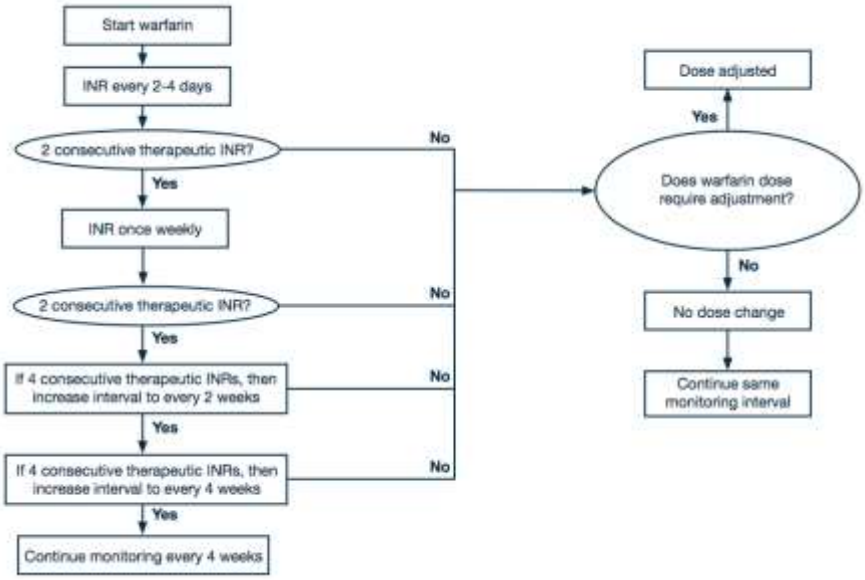

Fig. 3: Recommended Frequency of INR Monitoring

Table 4: Warfarin Dosage Adjustments (Target INR 2.0 - 3.0 or 2.5 - 3.5, No Significant Bleeding)

INR	Intervention
≤ 1.5	Give one time top-up equal to 20% of weekly dose and increase weekly dose by 10-20%
1.5 < INR < therapeutic range	• No change in dose • If two consecutive INRs are low, increase weekly dose by 10-20%
INR in therapeutic range	No change
INR > therapeutic range but < 5.0	• Lower weekly dose (10-20%) or consider omitting one single dose • Increase the frequency of INR monitoring and resume therapy at 10 - 20% lower weekly dose when INR therapeutic
INR 5.0 – 9.0*	• Omit 1 to 2 doses then recheck INR • Increase the frequency of INR monitoring and resume therapy at 10-20% lower weekly dose when INR therapeutic • If the patient is at high risk of serious bleeding, consider administering vitamin K** 1 to 2 mg orally
>9.0; no bleeding	• Discontinue warfarin temporarily, administer vitamin K i.v. then recheck INR** • Increase the frequency of INR monitoring and resume therapy at 20% lower weekly dose when INR therapeutic • Give additional vitamin K if INR is not substantially reduced by 24 hrs**

* Bleeding risk increases exponentially from INR 5.0 to 9.0 and should be monitored closely **avoid IM injections. The effect of a single dose of vitamin K on the INR can be expected between 8-24 hours.

Non-warfarin oral anticoagulants/ Direct oral anticoagulants (DOACs)

Non-warfarin oral anticoagulants, also called direct oral anticoagulants (DOACs), are available as alternatives to as a 1st-line treatment forthe treatment of DVT and PE; not all DOACs are currently FDA-approved for this indication. Drugs include factor Xa inhibitors (rivaroxaban, apixaban) and a direct thrombin inhibitor (dabigatran). Compared to coumarins, these drugs have been shown to give similar protection against recurrent DVT and have similar risk of serious bleeding.Their advantages are that they are effective within several hours, and they are given as a fixed dose (thus do not require ongoing laboratory testing). Their disadvantages are that they are expensive, and currently thereare no available antidotes to reverse their anticoagulant effect in patients withmajor bleeding or who need urgent surgery. If used, rivaroxiban 15 mg orally bid is started immediately upon diagnosis and given for 3 wk followed by 20 mg orally once/day for 9 weeks. Apixaban 10 mg orally bid is started immediately upon diagnosis and given for 7 days followed by 5 mg orally bid for 6 months. Dabigatran150 mg orally bid is given only after an initial 5 to 7 days of treatment with LMWH[10,11].

Duration of treatment

Patients with transient risk factors for DVT (eg, immobilization, surgery) can usually stop taking after 3 to 6 months Patients with non-modifiable risk factors (eg, hypercoagulability), idiopathic (or unprovoked) DVT with no known risk factors, or recurrent DVT should takefor at least 6 months and, in selected patients, probably for life unlesscomplications occur[10].

Bleeding is the most common complication. **Risk factors** for severe bleeding (defined as life-threatening hemorrhage or loss of ≥ 2 units of blood in ≤ 7 days) include age ≥ 65; history of prior GI bleeding or stroke; recent MI; and coexisting anemia (Hct< 30%), renal insufficiency (serum creatinine> 1.5 mg/dL), or diabetes. In patients who are actively bleeding or may be at increased risk of bleeding, anticoagulation can be reversed with vitamin K; the dose is 1 to 2.5 mg po if INR is 5 to 9, 2.5 to 5 mg orally if INR is > 9, and 5 to 10 mg IV (given slowly to avoid anaphylaxis) if hemorrhage occurs. If hemorrhage is severe, a transfusion of coagulation factors, fresh frozen plasma, or prothrombin complex concentrate (PCC) should also be given. Selected patients with over anticoagulation (INR 5 to 9) who are neither actively bleeding nor atincreased risk of bleeding can be managed by omitting 1 or 2 dosesand monitoring INR more frequently, then giving at a lower dose. Rarely, warfarin causes skin necrosis in patients with protein C or S deficiency or factor V Leiden mutations[1,2,9,10].

Lytic Therapy

Lytic therapy refers to administration of streptokinase, urokinase, or tissue-Plasminogen Activator (t-PA), all of which act on the endogenous fibrinolytic system to convert plasminogen to plasmin. Streptokinase combines with plasminogen to form streptokinase-plasminogen complexes that are converted to streptokinase-plasmin complexes, which then convert residual plasminogen to plasmin. Urokinase directly cleaves a peptide bond in the plasminogen molecule to form plasmin. t-PA binds to fibrin via lysine binding sites at the N-terminal[1,2].

Indications and contraindications

Lytic therapy is most effective when it can be initiated within hours. It is worth attempting when the clot has been present for less than 3 days. Lytic therapy is useful for symptomatic DVT of major upper-extremity veins. The morbidity of axillary vein thrombosis can be considerable; clearance of clot may not only help restore patency but also help identify the underlying cause. In the lower extremities, more thorough clearance of clot should, in theory, help restore valve function and prevent so-called postphlebitic syndrome.[1,2]

When lytic therapy is begun, heparin therapy usually is temporarily discontinued because of the theoretical possibility of increased bleeding risk; it may be resumed immediately upon completion of lytic therapy. If, however, the problem is immediately life-threatening (e.g., myocardial infarction or massive PE), anticoagulation should probably be done in parallel with lytic therapy to prevent re-thrombosis.

Contraindications to lytic therapy include surgery in the previous 10 days, serious GI bleeding in the previous 3 months, a history of hypertension, an active bleeding or hemorrhagic disorder, a previous

cerebrovascular accident, and an active intracranial process. As with heparin, the risk of intracranial bleeding is increased in older patients; the risk appears to be higher with t-PA than with streptokinase or urokinase.

Surgery for DVT

Surgery is rarely needed. However, thrombectomy, fasciotomy, or both are mandatory for phlegmasia alba dolens or phlegmasia cerulean dolens unresponsive to thrombolytics to try to prevent limb-threatening gangrene[2].

Prevention

Prevention of DVT in patients can be done by prevention of immobility, assessment of risk, anticoagulation (e.g. LMWH), and use of intermittent pneumatic compression devices[9].

Patients at low risk of DVT (e.g, those who are undergoing minor surgery but have no clinical risk factors for DVT, those who must be temporarily inactive for long periods, as during an airplane flight) should be encouraged to walk or otherwise move their legs periodically; no medical treatment is needed. Dorsiflexion 10 times/h is probably sufficient[1,10].

Table 5: Risk of Deep Venous Thrombosis and Pulmonary Embolism in Surgical Patients

Risk Category	***Examples***	***Preventive Measures***	***Risk of DVT (%)***	
			Calf	PE
Low	1. Nonmajor surgery* in patients < 40 yr with no clinical risk factors	Early and aggressive ambulation	2	0.2
Moderate	1. Nonmajor surgery in patients with risk factors 2. Minor surgery in patients 40–60 yr with no clinical risk factors 3. Major surgery in patients < 40 yr with no other clinical risk factors Immobilized patients with major medical illnesses	LMWH, Fondaparinux, or IPC, with or without elastic stockings	10-20	1-2
High	1. Nonmajor surgery in patients > 60 yr or 40–60 with risk factors 2. Major surgery in patients > 40 yr or with other clinical risk factors	LMWH, Fondaparinux, or IPC	20-40	2-4
Very high	1. Major surgery in patients > 40 yr who have had a previous venous thromboembolic, malignant, or hypercoagulability disorder 2. In patients of any age: Hip or knee arthroplasty Hip fracture surgery Elective neurosurgery Multiple trauma Spinal cord injury	LMWH, oral anticoagulation, IPC, or elastic stockings plus LMWH. Fondaparinux if patients have had orthopedic, abdominal, or thoracic surgery or have an acute, severe illness	40-80	4-10

*Nonmajor surgery is defined here as an operation that does not involve general anesthesia or respiratory assistance.

DVT = deep venous thrombosis; PE = pulmonary embolism; LMWH = low molecular weight heparin; IPC = intermittent pneumatic compression.

Patients at higher risk of DVT include those undergoing minor surgery if they have clinical risk factors for DVT; those undergoing major surgery, especially orthopedic surgery, even without risk factors; and bedbound patients with major medical illnesses (eg, most critical care unit patients, other patients with heart failure, COPD, chronic liver disease, stroke). These patients require additional preventive treatment (see Table 5: Risk of Deep Venous Thrombosis and Pulmonary Embolism in Surgical Patients). Most of these patients can be identified and should receive DVT prophylaxis[9,10].

After surgery, elevating the legs and avoiding prolonged immobility, which places the legs in a dependent position thereby impeding venous return, can help. Additional treatment may involve low-dose Heparin, LMWH, new oral anticoagulants, compression devices or stockings, or a combination, depending on patient's risk level, type of surgery (if applicable), projected duration of preventive treatment, contraindications, adverse effects, relative cost, ease of use, and local practice. LMWHs are more effective than low-dose Heparin for preventing DVT and PE, but widespread use is limited by cost.

Enoxaparin 30 mg sc every 12 h, Dalteparin 5000 units sc once/day, and Tinzaparin 4500 units sc once/day appear to be are equally effective. Fondaparinux 2.5 mg sc once/day is at least as effective as LMWH in patients who are undergoing nonorthopedic surgery and is possibly more effective than LMWHs after orthopedic surgery[9,10].

For patients who are at very high risk of venous thromboembolism and bleeding (eg, after major trauma) IPC is recommended until the bleeding risk subsides and anticoagulants can be given. The use of IVCF should be avoided unless DVT has been confirmed, except in highly selected patients[9,10].
Intermittent pneumatic compression (IPC) uses a pump to cyclically inflate and deflate hollow plastic leggings, providing external compression to the lower legs and sometimes thighs. IPC may be used instead of or in combination with anticoagulants after surgery. IPC is recommended for patients undergoing surgery associated with a high risk of bleeding in whom anticoagulant use may be contraindicated. IPC is probably more effective for preventing calf than proximal DVT[9,10].

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Management of Complications of Deep Vein Thrombosis

Pawan Lal

Risk factors for Deep vein thrombosis

1. Age – because of
    a. soleal veins age they lose their elasticity and the resuling dilatation and tortuosity contributes to an increase in the stasis of the blood,
    b. the decrease in muscle mass of the venous pump results in decreased pump effectiveness and additional venous stasis
    c. increased incidence of associated conditions and diseases for example heart diseases, diabetes, malignancy etc.
2. Sex- females are more prone to develop DVT because of estrogens, pregnancy
3. Heart disease
4. Malignancy
5. Trauma
6. Sepsis
7. Hypercoaguable state
8. Previous history of deep vein thrombosis

Clinical tests

Moses test – compression of the calf muscles is positive in DVT

Homan's sign – pain in the calf with forced dorsiflexion of the foot is non-specific for the diagnosis of DVT as it occurs in other conditions as well.

Investigations

- Doppler study of the limb – Duplex ultrasound
- Radioactive fibrinogen uptake – I^{125} fibrinogen gets incorporated into the thrombus and is detected by external scintigraphy
- Venography – ascending phlebography and descending phlebography

Thrombus formation

Virchows triad – three conditions are necessary for the thrombus formation

- Damage to wall of vein
- Slowing of flow of blood in vein
- Change in constitution of blood

(That is stasis, venous injury and increased coaguability)

Incidence – 0.1 to 0.2 % fatal embolism

Thrombus formation usually begins in valve pockets where areas of maximum stasis occurs or at sites of venous injury. Deep venous thrombosis occurs most often in the calf veins especially the soleal veins.

Thrombosis is more common in left lower extremity and may be related to compression of the left common iliac vein by the right common iliac artery (**May-Thurner syndrome**).

Thrombus formation

Stage I – platelet formation – Gray amorphous semitransparent process stops here or progresses depends upon vessel diameter, speed of blood flow, and possibly changes in fibrinogen and clotting factors.

Stage II – coralline thrombus. Series of outpouching corrugted parallel laminae composed of hyalinised platelets which grow across the stream and are bent in the direction of flow.

Propagated thrombus – consecutive thrombosis along long length of the vessel due to sluggish flow. It contracts and then a thrombus remains just attached at its beginning – this is the most dangerous stage- high chances of thromboembolism. This silent dangerous stage is called as phlebothrombosis.

Embolus – is a plug, composed of a detached thrombus or vegetation, mass of bacteria, or other foreign body, occluding a vessel.

Pulmonary embolism

Cause of death in pulmonary embolism – gross dilatation of the heart with decreased blood flow to the heart with decreased output – inadequate coronary flow – ventricular fibrillation of the heart.

Clinical guide to spread of thrombus

Stage I – thrombus confine to calf sinusoids – calf tenderness on deep palpation
Stage II – spread of thrombus to involve posterior tibial vein and ankle perforator

- Calf tenderness and Homan's sign
- Tenderness and edema on inner aspect of ankle or lower leg
- Low pyrexia
- Warm ankle
- Duskiness of foot in dependent position

Stage III – spread to the thrombus to posterior tibial vein and popliteal vein

- Marked edema of ankle
- Increase in girth of calf
- Leg is obviously warm to touch
- Pyrexia is 99 – 100 F

Stage IV – spread to involve whole of femoral and iliac veins

- Picture of white leg – phlegmesia alba dolens
- Concentric tense edema of whole limb
- Limb pale and dusky blue
- Limb hot to touch
- Fever > 101 F
- Limb heavy – moved and flexed with difficulty

Ilio-femoral thrombosis

Acute obstruction of external iliac vein – limb becomes white and cold (plegmasia alba dolens), rapidly replaced by blue warm tensely swollen painful limb due to superficial dilatation of all small veins (Phlegmasia cerulea dolens).

Treatment of ilio-femoral thrombosis

1. Ligation of the common iliac or inferior vena cava – should never be done as it causes excessive fluid retention in legs (shock like state). It recovers to gross swelling and congestion of both legs. Only situation where it can be done without sequalae is left iliac compression syndrome as it already has collateral well developed.

2. Plication of the inferior vena cava – operation of choice
    a. Sepncer method – divides IVC into multiple channels
    b. De weese method – silk suture net technique
    c. Maretz technique – external plastic clips of various sizes.

3. Filter – umbrella like filters are placed in inferior vena cava below the level of renal vessels transvenously– for example Green filter, Mobbin uddain filter etc.

Phlegmasia alba dolens – incomplete venous obstruction, leg is edematous and tense. In phlegmasia alba dolens the less severe form of phlegmasia the extremity is edematous and pale but not ischemic, neural functions are normal.

Phlegmasia cerulea dolens – complete venous obstruction, leg is cyanosed and gangrenous. The extremity often exhibits petechiae and bullae. The extremity is at risk for arterial insufficiency and neural compression with the development of sensory and motor deficits of the distal leg.

Post-Thrombotic Syndrome

Type I – infra-inguinal type (most common) – recanalization of the vessels takes place after thrombosis but there is venous destruction of the valves. Venous incompetence leads to ankle changes. Problem is basically below the knee.

Type II – Supra-inguinal type – segmental iliofemoral thrombosis. Do not recanalize well. Infrainguinal valves and perforators are normal. Present with swelling of the thigh and may be calf. Chronic edema of muscles – hypertrophic picture. **Venous claudication** is positive as not very much collaterals are present. Uterine, parametrial and ovarian vessels collateralize blood $\rightarrow$ menorrhagia and dysmenorrhia (severe). Men lack such collaterals therefore symptomatic early.

Type III combined – more severe therefore symptomatic early. Valve and perforator incompetence with iliofemoral thrombosis, which leads to severe intractable thrombosis.

Prophylaxis

1. Compression devices – elastic stockings and pneumatic compression devices
2. Subcutaneous heparin – 5000 units subcutaneously every 8 – 12 hours postoperatively
3. Low molecular weight heparin
4. Warfarin – inhibits the liver's synthesis of active vitamin K dependent coagulation factors II, VII, IX and X. Decreases in factors activity depends upon the circulating half life of the factors VII which reaches steady state after 1 – 2 days and prothrombin (factor II) takes up to 10 days. Side effects – hemorrhage, dermatitis, alopecia, hypersensitivity and diarrhoea. Contraindicated in pregnancy due to teratogenic effects. Effects reversed by vitamin K or fresh frozen plasma.
5. Dextran – low molecular weight dextran 40 or dextran 70. decrease platelet adhesiveness and alters the release reaction causing decreased aggregation. Dose – 500m of 6% solution to 1000 ml of 10% solution per 24 hours can be given. Side effects – pulmonary edema secondary to volume expansion, hemorrhage, renal failure and anaphylactoid reactions.

Treatment

1. Heparin – is the first line of treatment. Dose – 5000 – 20000 units IV heparin bolus with continous IV infusion 6000 units 6hrly. And is adjusted to keep APPTK at least 1.5 times control values. IV heparin therapy is continued for 4 – 6 days (when oral anticoagulation is started with warfarin on second or third day of beginning of heparin therapy).
2. Thrombolytic therapy with streptokinase or urokinase. Best results are obtained in patients who had symptoms less than 48 hours of duration.
3. Surgery –
    - Thromboembolectomy – rarely done – indications are contraindication to coagulation therapy and imminent lower limb gangrene
    - Occlusion of inferior vena cava – placement of Greenfield filter in IVC below the origin of renal vessels transvenously.

Pulmonary embolism

The classic triad of symptoms – dyspnoea, hemoptysis and pleuritic chest pain. Tachypnea is the most common finding associated with pulmonary embolism.

Essentials of Clinical diagnosis

- Dyspnoea
- Hemoptysis
- Pleuritic pain
- Tachycardia
- Clinical thrombophlebitis
- Atypical asthma

Investigations

X-rays findings – westerkmarks sign (hyperlucency in an area of oligemia)

Pulmonary perfusion scans (ventilation perfusion scan) – most useful diagnostic technique. Reduced perfusion in areas that appear normal on chest radiograph is suggestive of pulmonary embolism.

A scan that demonstrates a decrease in ventilation and perfusion in the same lung area indicates airway or parenchymal disease, whereas a normal ventilation scan and an abnormal perfusion scan in the proper clinical setting are highly suggestive of pulmonary embolism.
Pulmonary angiography is the most reliable test for establishing the diagnosis of pulmonary embolism.

Biochemical / Laboratory tests

Triad of elevated lactic dehydrogenase, bilirubin and normal serum glutamic oxalic transaminase. Blood gas anaysis shows degree of hypoxemia with low carbon dioxide pressures because of hyperventilation.

Treatment

Medical – supportive treatment. Aggressive fluid administration to increase the filling of the left atrium and thus improve cardiac output.

Anticoagulation – heparin remains the principal agent for treating pulmonary embolism. Dose for adult patient is 10,000 to 20,000 U heparin as the initial dose and 800 – 1000 U per hour during diagnostic evaluation. After 24 to 48 hours apt is maintained at 1.6 to 1.8 times that of the control. IV heparin is continued for 5 to 10 days and warfarin is started and continued for minimum of 3 months.

Thrombolysis – patients die from massive pulmonary embolism because right ventricular failure secondary to sudden increase in pulmonary vascular resistance caused by embolism. Is useful in early resolution of thrombus when administered within 12 hours of embolism.

Surgical therapy – operative embolectomy has been reserved for the patient with massive pulmonary embolism and cardiac collapse. The diagnosis of pulmonary embolism must be confirmed by angiography before operative intervention. The operative mortality rate for embolectomy is about 50%.

To prevent further pulmonary embolism or impending pulmonary embolism as in illio-caval thrombosis the occlusion of inferior vena cava can be done or placement of Greenfield filter in IVC below the origin of renal vessels transvenously can be considered depending on the condition of the patient and available resources.

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Diabetic Foot

Ashok K. Attri

Introduction

Diabetes mellitus is one of the most critical health conditions around the world, not only in terms of the number of affected people, disability and premature mortality but also in regards to the health care costs involved in controlling and treating its complications.[1] The prevalence of diabetes mellitus is increasing in epidemic proportions. The worldwide prevalence of diabetes now exceeds 200 million and is expected to rise to more than 300 million in the next 20 years.[2-4]India is considered as the diabetic capital of the world and accounts for approximately 12.5-15% of all the patients globally.

It is well known that diabetic patients have a high risk of developing complications including retinopathy, nephropathy, cardiovascular diseases, neuropathy and diabetic foot ulcer. Diabetic foot is the commonest complication among diabetics, which is defined as any infection, ulceration, and/or necrosis of deep tissues associated with neurological abnormalities and various degrees of peripheral vascular disease of the lower limbs. Approximately 10-15% of diabetic patients run the risk of developing ulcers. The major contributors to the formation of diabetic ulcers includes neuropathy, foot deformity and ischemia.[6]

Diabetic foot is now a well-established leading cause of non-traumatic lower extremity amputations world over, frequently contributing to the morbidity. The International Working Group on the Diabetic Foot (IWGDF)estimates that the loss of a foot or leg attributable to diabetes occurs every 30 seconds in the world. In addition, these foot complications in diabetic patients inflict an enormous financial burden on the society, since amputations are associated with substantial direct (hospitalization and medication) as well as indirect (loss of working days) costs.[2]

There are various classification systems for diabetic foot ulcers. The commonly used are Wagner-Meggitt classification which defines wounds by depth of ulceration and extent of gangrene. The

University of Texas system grades wounds by depth and then stages them by the presence or absence of infection and ischemia. More recently, the International Working Group on the Diabetic Foot has proposed the PEDIS classification, which grades the ulcer on the basis of perfusion (arterial supply), extent (area), depth, infection and sensation.

Infection often complicates the pathological picture of diabetic foot and plays a main role in development of moist gangrene. Sustaining a foot wound/injury is invariably an antecedent event leading to foot infections. These infections most commonly involve soft tissue but may penetrate to underlying bones. Most of the times diabetic foot infections are poly-microbial. Among the most frequently isolated microorganisms are *Staphylococcus aureus,* Group B Streptococci*, Enterococci* species*,* anaerobic bacteria including *Bacteriodes fragilis* and some enteric gram negative bacilli like *Pseudomonas* species, *Klebsiella* species, *Escherichia coli*, *Proteus mirabilis,* etc.

Patients with infected diabetic foot are managed with extensive surgical debridement of necrosed/infected tissue, effective antibiotics therapy, empirical initially and then according to culture and sensitivity.[7]

There has been a recent emergence of multidrug resistant organisms (MDRO) associated with diabetic foot infection (DFI) which further complicates the management of Diabetic foot syndrome. Recurrent and deep ulcer, previous hospitalization and poor glycemic control are risk factors for developing drug resistant organisms. Most commonly encountered MDRO are Methicillin resistant *Staphylococcus aureus* (MRSA), Vancomycin resistant Enterococci (VRE) and Gram-negative bacteria producing Extended spectrum beta lactamases (ESBL), Metallo beta lactamases (MBL). These infections require targeted antibiotic therapy for longer durations, leading to longer hospital stay and cost. These may also lead to minor and major amputations.

Morbidity and mortality in DFI is often associated with severity of infection, presence of peripheral arterial disease, duration of infection, poor glycemic control and presence of comorbid conditions.

Early diagnosis of microbial infections is aimed to institute appropriate antibacterial therapy and prompt surgical management is required for favorable outcome to avoid further complications.[8, 9]

Diabetic foot

The WHO defines diabetes mellitus as a metabolic disorder with heterogeneous etiologies, which is characterized by chronic hyperglycemia and disturbances of carbohydrate, fat and protein metabolism, resulting from defects in insulin secretion, insulin action or both. The prevalence of diabetes for all age groups worldwide was estimated to be 2.8% in 2000and 4.4% in 2030. In India there were 31.7 million cases of diabetes in year 2000 and this number is expected to rise to 79.4 million in year 2030.[4]

The term ‘Diabetic Foot’ consists of a mix of pathologies including diabetic neuropathy, peripheral vascular disease, Charcot’s neuroarthropathy, foot ulceration, osteomyelitis and the potentially preventable endpoint, limb amputation.[12]Diabetic foot ulceration and infections are a major medical, social, economic problem and a leading cause of morbidity and mortality, especially in the developing countries like India.[10, 11]

Epidemiology of diabetic foot

Diabetic foot complications are more frequent in males and individuals over 60 years. Based on recent studies, the annual population based incidence for diabetic ulcers is 1-4%, with a prevalence of 4-10%. The lifetime risk is estimated to be ~25%.[13]

Definition of diabetic foot infection

As all chronic wound wounds are colonized by microorganisms. The diagnosis of DFI should not be based only on the microbiological analysis of a wound culture but also on clinical findings.

As per the Infectious Diseases Society of America (IDSA), DFI is defined by the presence of at least two inflammatory manifestations (purulence or erythema, pain, tenderness, warmth or induration) and

divided according to severity as mild, moderate and severe infection, according to the extent of tissue involvement and presence of systemic toxicity or metabolic derangement.[14]

Pathophysiology of diabetic foot infections

Several factors predispose diabetic patients to developing a DFI, including neuropathy, vasculopathy and immunopathy. Peripheral neuropathy occurs early in the pathogenesis of diabetic foot complications and is considered the most prominent risk factor for diabetic foot ulcers.[13] Diabetic patients with impaired protective sensation and altered pain response are vulnerable to trauma and extrinsic forces from ill-fitting shoe wear. Motor neuropathy causes muscle weakness and intrinsic muscle imbalance leading to digital deformities such as hammered or clawed toes. This results in elevated plantar pressure due to metatarsophalangeal joint instability. Autonomic dysfunction leads to changes in micro vascular blood flow and arteriolar-venous shunting, diminishing the effectiveness of perfusion and elevating skin temperatures. With the loss of sweat and oil gland function, the diabetic foot becomes dry and keratinized which cracks and fissures more easily, leading to a portal for infection.[15]

Diabetic angiopathy is reported to be the most frequent cause of morbidity and mortality in diabetic patients.[16] Macroangiopathy manifests as a diffuse multi-segmental involvement typically involving the infrapopliteal vessels, and is also associated with collateral circulation. This is considered an atherosclerotic obstructive disease of large vessels, which leads to peripheral arterial disease (PAD) of the lower extremities. In a case controlled study of 112 hospitalized diabetic patients by Peters et al, PAD was independently associated with a 5.5 fold increased risk for DFI.[17]Microangiopathy results in capillary basement membrane thickening, altered nutrient exchange, tissue hypoxia and microcirculation ischemia. An ABI value of <0.90 or >1.30 is indicative of PAD; with the latter significant for falsely elevated values secondary to medial arterial calcification.[18]

A normal toe brachial index(TBI) of>0.7 has been shown to be superior to ABI for excluding the presence of PAD as calcification is not usually present in digital vessels. Another clinical test that can be performed, regardless of arterial calcification in major pedal arteries, includes transcutaneous oxygen (TcPO2) tension measurements. Although not highly prognostic of wound healing potential, TcPO2s are predictive of wound healing failure at levels below 25 mmHg.[18]

Immunopathy has been implicated in the diabetic patient's inherent susceptibility to infection as well as the potential to mount a normal inflammatory response. Impaired host defences secondary to hyperglycaemia include defects in leukocyte function and morphologic changes to macrophages. Bagade et al demonstrated that leukocyte phagocytosis was significantly reduced in patients with poorly controlled diabetes and improvement of microbicidal rates was directly correlated with correction of hyperglycemia.[19]

Osteomyelitis of the foot in diabetic patients

Osteomyelitis of the foot, a common and serious problem in diabetic patients, results from diabetes complications, especially peripheral neuropathy. Infection generally develops by spread of contiguous soft-tissue infection to underlying bone. The major diagnostic difficulty in diabetic patients is distinguishing bone infection from non-infectious neuropathic bony lesions. Certain clinical signs suggest osteomyelitis, but imaging tests are usually needed.[20, 21]
One bedside clinical test for detecting osteomyelitis underlying an open wound is "probe to bone test" which according to a study has a positive predictive value of 89% and a negative predictive value of 56%.[32]

The ^{111}In-labeled leukocyte scan and magnetic resonance imaging are the most sensitive means to diagnose osteomyelitis. *Staphylococcus aureus* is the most common etiologic agent, followed by other aerobic gram-positive cocci. Aerobic gram-negative bacilli and anaerobes are occasionally isolated, often in mixed infections.[20,21]

Risk factors for diabetic foot infections
Risk factors for DFU are clearly defined in the current literature. Significant independent risk factors for DFI includes (1) wounds that penetrated to bone, (2) wounds with the duration >30 days, (3) recurrent wounds, (4) wounds with a traumatic etiology and (5) the presence of PAD. Other published

studies associate neuropathy and history of previous amputations as significant risk factors for infection. Socioeconomics demographics and other clinical characteristics such as elevated body mass index (BMI) and duration of diabetes have not been found to be significantly associated with DFI.[19]

Classification system for diabetic foot ulcers
Various classification systems for diabetic foot ulcer are used world over, most commonly used are:

1. Wagner Grading System[22]

Grade 1: Superficial Diabetic Ulcer
Grade 2: Ulcer extension
Involves ligament, tendon, joint capsule or fascia
No abscess or Osteomyelitis
Grade 3: Deep ulcer with abscess or Osteomyelitis
Grade 4: Gangrene to portion of forefoot
Grade 5: Extensive gangrene of foot

2. University of Texas classification for diabetic foot wound[23]

Staging
Stage A: No infection or ischemia
Stage B: Infection present
Stage C: Ischemia present
Stage D: Infection and ischemia present
Grading
Grade 0: Epithelialized wound
Grade 1: Superficial wound
Grade 2: Wound penetrates to tendon or capsule
Grade 3: Wound penetrates to bone or joint

3. IWGDF-IDSA (International Working Group on Diabetic Foot Infectious Diseases Society of America) Classification[14]

IDSA defined Infection by presence of at least 2 of the following:

- Local swelling or induration
- Erythema
- Local tenderness or pain
- Local warmth
- Purulent discharge (thick, opaque to white or sanguineous secretion)

Clinical description	IDSA infection severity
No symptoms or signs of infection	Uninfected
Local infection involving only the skin and subcutaneous tissue (without involving deeper tissues and without systemic signs) if erythema must be > 0.5 cm to less than equal to 2 cm around the ulcer	Mild
Local infection with erythema >2 cm, or involving structures deeper than skin and subcutaneous tissue (e.g. abscess, osteomyelitis, fasciitis, septic arthritis) and no systemic inflammatory response signs	Moderate
Local infection with signs of SIRS, as manifested by greater than 2 of the following: • Temperature >38°C or <36°C • Heart rate >90/min • Respiratory rate >20/min or $PaCO_2$ <32 mm Hg • WBC count >12000 or <4000/microlitre or greater than equal to 10% immature (band) forms	Severe

Bacteriology of diabetic foot infections

Predominantly the diabetic foot infections are mixed bacterial infections, with aerobic Gram- positive-cocci (GPC) especially *Staphylococci aureus*, being the most common causative organism. Aerobic

gram negative bacilli are frequently isolated as co-pathogens in infections that are chronic or follow antibiotic treatment, and additionally obligate anaerobes are also associated with aerobic bacterial isolates in ischemic or necrotic wound.[24]In a study of 84 randomly selected hospitalized patients with severe DFI, 83% of cultures demonstrated poly-microbial flora with an average of 2.8 species per specimen and aerobic to anaerobic bacteria ratio of 3:1.[25] The most frequent isolated organisms were *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Streptococcus* species. Among anaerobes, *Peptostrptococcus magnus* and *Bacteriodes fragilis* were noted. Calhoun et al[31] found that aerobic gram-positive cocci were the most common organisms isolated from diabetic wounds in various studies, especially DFI that were identified as *Staphylococcus aureus,* Group B streptococci*,* Enterococcus species. *Pseudomonas aeruginosa* may be isolated in macerated wounds whereas obligate anaerobes are commonly present in necrotic or gangrenous infections.[7]According to another study the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in DFI, among hospitalized patients was 15-30% depending on the geography.[15]The proper management of these infections requires appropriate antibiotic selection based on culture and antimicrobial susceptibility testing. Sometimes, initial management comprises of empirical antimicrobial treatment based on susceptibility data. Currently, there was paucity of data on ESBL and MBL-producing organisms from diabetic foot infections especially from our geographical area.

In a patient exposed to antibiotics, resistant organisms may emerge by natural selection through the expansion of sub-population generated spontaneously.[26]According to few researchers the multi drug resistant organisms of greater importance in the hospital environment include methicillin-resistant *Staphylococcus aureus,* vancomycin-resistant enterococcus species (VRE)*,* and multi-drug resistant gram-negative bacteria includes *Pseudomonas* species, *Acinetobacter* species, *Escherichia coli, Klebsiella pneumonia, Proteus* species, *Enterobacter* species and other organisms.[27] Given this resistance's panorama, it is necessary to determine the bacteriological profile of admitted patients in a hospital settings and also determine the bacteriological profile of hospitalized patients in order to reduce the high rates of amputation and in hospital morality rate in the people with diabetes and foot ulcer.[28]

Outcome in patients with DFI with MDRO

Infection with multidrug resistant organisms (MDRO) may increase the duration of hospital stay, cost of management and may cause additional morbidity and mortality.[27]

Richard et al in their study evaluated the risk factors and impact of MDRO in diabetic foot ulcers.[29] They observed an incidence of 23.9% of MDRO in 188 patients studied. Deep and recurrent ulcers, previous hospitalization, HbA1c levels, nephropathy and retinopathy were significantly associated with MDRO-infected ulcers but the presence of MDR bacteria had no significant impact on healing time of ulcers.[29]

Similarly Game et al (2003)[30] and Hartemann et al (2004)[27] did not find any significant difference in the healing rate.

According to Eckman et al mortality from infections with MDR organisms is twice as high as mortality from infections with microorganisms sensitive to antibiotics.[34]

The effect of presence of MDRO on ultimate outcome of diabetic foot infection is controversial and needs to be evaluated.

Recommendations for managing diabetic foot infections[24]

1. Clinicians should consider the possibility of infection occurring in any foot wound in a patient with diabetes.
2. Clinicians should be aware of factors that increase the risk for DFI and especially consider infection when these factors are present; these include a wound for which the probe-to-bone (PTB) test is positive; an ulceration present for >30 days; a history of recurrent foot ulcers; a traumatic foot wound; the presence of peripheral vascular disease in the affected limb; a previous lower extremity amputation; loss of protective sensation; the presence of renal insufficiency; or a history of walking barefoot .

3. Clinicians should select and routinely use a validated classification system, such as that developed by the International Working Group on the Diabetic Foot (IWGDF) (abbreviated with the acronym PEDIS) or IDSA .
4. We recommend assessing the affected limb and foot for arterial ischemia , venous insufficiency, presence of protective sensation, and biomechanical problems .
5. We recommend that clinicians unfamiliar with pressure off-loading or special dressing techniques consult foot or wound care specialists when these are required .
6. We recommend that all patients with a severe infection, selected patients with a moderate infection with complicating features (eg, severe peripheral arterial disease [PAD] or lack of home support), be hospitalized initially.
7. For clinically uninfected wounds, we recommend not collecting a specimen for culture .
8. We recommend that clinically uninfected wounds not be treated with antibiotic therapy .
9. We recommend prescribing antibiotic therapy for all infected wounds.
10. We recommend that clinicians select an empiric antibiotic regimen on the basis of the severity of the infection and the likely etiologic agent(s) .
    - For mild to moderate infections in patients who have not recently received antibiotic treatment, we suggest that therapy just targeting aerobic GPC is sufficient.
    - For most severe infections, we recommend starting broad-spectrum empiric antibiotic therapy, pending culture results and antibiotic susceptibility data .
    - Empiric therapy directed at Pseudomonas aeruginosa is usually unnecessary except for patients with risk factors for true infection with this organism .
    - Consider providing empiric therapy directed against methicillin-resistant Staphylococcus aureus (MRSA) in a patient with a prior history of MRSA infection; when the local prevalence of MRSA colonization or infection is high; or if the infection is clinically severe .
11. We suggest basing the route of therapy largely on infection severity. We prefer parenteral therapy for all severe, and some moderate, DFIs, at least initially , with a switch to oral agents when the patient is systemically well and culture results are available.
12. We suggest continuing antibiotic therapy until, but not beyond, resolution of findings of infection, but not through complete healing of the wound. We suggest an initial antibiotic course for a soft tissue infection of about 1–2weeks for mild infections and 2–3 weeks for moderate to severe infections
13. We recommend that all patients presenting with a new DFI have plain radiographs of the affected foot to look for bony abnormalities (deformity, destruction) as well as for soft tissue gas and radio-opaque foreign bodies .
14. Clinicians should consider osteomyelitis as a potential complication of any infected, deep, or large foot ulcer, especially one that is chronic or overlies a bony prominence
15. We suggest doing a PTB test for any DFI with an open wound.
16. Clinicians can consider using either primarily surgical or primarily medical strategies for treating DFO in properly selected patients .
17. When a radical resection leaves no remaining infected tissue, we suggest prescribing antibiotic therapy for only a short duration (2–5 days) . When there is persistent infected or necrotic bone, we suggest prolonged (≥4 weeks) antibiotic treatment .
18. Diabetic patients with a foot wound should receive appropriate wound care, which usually consists of the following:
    - Debridement, aimed at removing debris, eschar, and surrounding callus . Sharp (or surgical) methods are generally best , but mechanical, autolytic, or larval debridement techniques may be appropriate for some wounds .
    - Redistribution of pressure off the wound to the entire weight-bearing surface of the foot (“off-loading”).
    - Selection of dressings that allow for moist wound healing and control excess exudation. The choice of dressing should be based on the size, depth, and nature of the ulcer (eg, dry, exudative, purulent) .
19. We do not advocate using topical antimicrobials for treating most clinically uninfected wounds.
20. No adjunctive therapy has been proven to improve resolution of infection, but for selected diabetic foot wounds that are slow to heal, clinicians might consider using bioengineered skin equivalents, growth factors, granulocyte colony-stimulating factors, hyperbaric oxygen therapy, or negative pressure wound therapy.

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Urinary Bladder Malignancy

Kim Mammen, Abhinav Jaiswal

Incidence

Bladder cancer is the second most common cancer of the genitourinary tract. It is the fourth most common cancer in men. Male-to-female ratio is 3.8:1. It accounts for 6.6% of the total cancers in men and 2.1% of total cancers in women. The incidence is higher in whites than in African Americans, and there is a positive social class gradient for bladder cancer in both sexes. The average age at diagnosis is 65 years. At that time, approximately 75% of bladder cancers are localized to the bladder; 25% have spread to regional lymph nodes or distant sites. Also at the time of Initial diagnosis of bladder cancer, 70% are non-muscle-invasive and 30% are muscle-invasive.

Risk Factors and Pathogenesis

- **Cigarette Smoking -** Cigarette smoking accounts for approx 50-65% of cases in men and 20–30% in women. In general, smokers have approximately a two- to threefold increased risk of bladder cancer than non-smokers, and the association appears to be time and dose related. The causative agents are thought to be alpha- and betanaphthylamine, which are secreted into the urine of smokers.
- **Occupational exposure -** Occupational exposure accounts for 20- 25% of cases. Workers in the chemical, dye, rubber, petroleum, leather, and printing industries are at increased risk. Specific occupational carcinogens include benzidine, beta-naphthylamine, and 4-aminobiphenyl.
- **Trauma -** Physical trauma to the urothelium induced by infection, instrumentation, and calculi increases the risk of malignancy.
- **EBRT –** Patients receiving external beam radiation therapy for gynaecological malignancies are at higher risk.
- **Dietary factors -** Vegetable and fruit intake reduces the risk of bladder cancer.
- **Chronic urinary tract infection –** Higher chances of invasive squamous cell carcinoma.
- **Schistosomiasis –** Schistosoma haematobium → formation of carcinogenic substance N-nitroso compounds → increased risk for both squamous and transitional cell Carcinoma.
- **Cyclophosphamide**
- **Genetics –** Retinoblastoma gene mutation
- **Bladder birth defects -** eg. persistent urachus → increase risk for adenocarcinoma. Urachus is a connection between belly button (umblicus) and bladder. Normally disappears before birth. If part of the connection remains, it could become cancerous. Cancers that start in the urachus are usually made up of malignant glandular cells and are called adenocarcinomas.

The genetic events leading to the development of bladder cancer are likely to be multiple and may involve the activation of oncogenes and inactivation or loss of tumor suppressor genes. Loss of genetic material on chromosome 9 appears to be a consistent finding in patients with both low-grade, low-stage and high-grade, high-stage disease (Miyao et al, 1993; Tsai et al, 1990). Also studies examining p53 tumor suppressor gene mutations in primary, recurrent, and upper-tract tumors suggest that these tumors can have a single clonal origin (Dalbagni et al, 2001; Sidransky et al, 1991). Chromosome 11p, which contains the c-Ha-ras proto-oncogene, is deleted in approximately 40% of bladder cancers (Olumi et al, 1990). Increased expression of the c-Ha-ras protein product, p21, has been detected in dysplastic and high-grade tumors but not in low-grade bladder cancers. Deletions of chromosome 17p have also been detected in over 60% of all invasive bladder cancers, but 17p deletions have not been described in superficial tumors. *TP53* alterations represent the most commonly identified genetic abnormality in human cancers, making deletion of this chromosome an important finding in carcinoma in situ (CIS) and muscle invasive bladder cancer. Mutations of the fibroblast growth factor receptor 3 (FGFr3) are found in >60% of papillomas and low-grade bladder tumors. Ras mutations are also found in both low- and high-grade or muscle invasive tumors but Ras and FGFr3 mutations appear to be mutually exclusive (Jebar et al, 2005) and both are involved in activation of the MAP Kinase pathway. p53 mutations are less common in low-grade tumors and loss of FGFr3 with increased expression of p53 has been associated with higher stage and grade (Knowles, 2007).

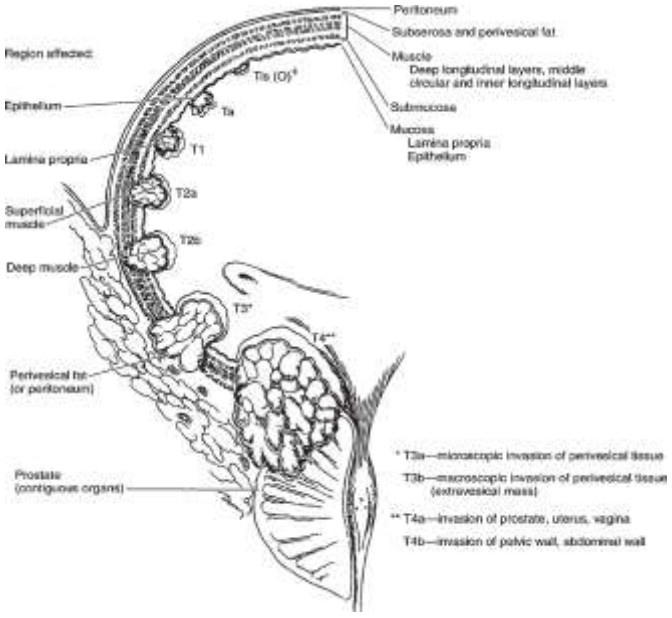
Staging

Currently, the most commonly used staging system allows for a precise and simultaneous description of the primary tumor stage (T stage), the status of lymph nodes (N stage), and metastatic sites (M stage) (*2009 TNM by UICC (Union International Contre le Cancer).* Staging errors exist when one compares the clinical stage (that based on physical examination and imaging) with the pathologic stage (that based on removal of the bladder and regional lymph nodes). Overstaging is relatively uncommon, but clinical understaging may occur in up to 53% of patients (Dutta et al, 2001; Skinner, 1982).

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ: 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate, uterus or vagina
T4b	Tumour invades pelvic wall or abdominal wall

N - Lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in greatest dimension
N2	Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension

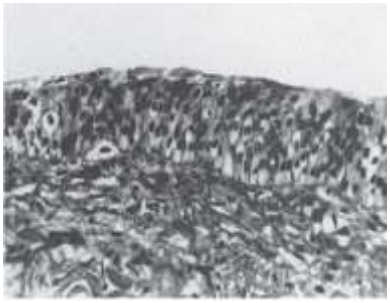
M - Distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis



Histopathology

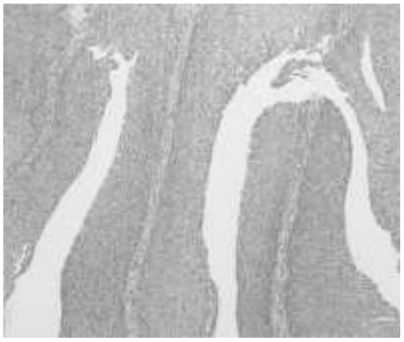
Ninety-eight percent of all bladder cancers are epithelial malignancies, with the predominant majority being transitional cell carcinomas (TCCs). About 5% are adenocarcinomas or squamous cell carcinomas.

A. Normal Urothelium



The normal urothelium is composed of 3–7 layers of transitional cell epithelium resting on a basement membrane composed of extracellular matrix (collagen, adhesive glycoproteins, glycosaminoglycans). The epithelial cells vary in appearance: The basal cells are actively proliferating cells resting on the basement membrane; the luminal cells, perhaps the most important feature of normal bladder epithelium, are larger umbrella-like cells that are bound together by tight junctions. Beyond the basement membrane is loose connective tissue, the lamina propria, in which occasionally smooth muscle fibers can be identified. These fibers should be distinguished from deeper, more extensive muscle elements defining the true muscularis propria.

B. Papilloma/PUNLMP

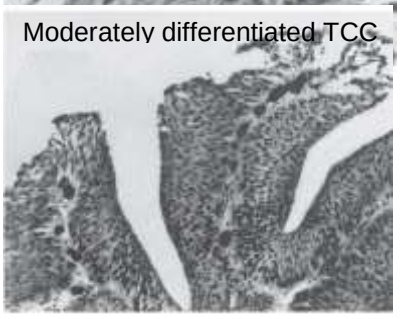


The World Health Organization recognizes a papilloma as a papillary tumor with a fine fibrovascular stalk supporting an epithelial layer of transitional cells with normal thickness and cytology (Epstein et al, 1998). These are also termed papillary urothelial neoplasms of low malignant potential or PUNLMP. The PUNLMP are defined as lesions that do not have cytological features of malignancy but show normal urothelial cells in a papillary configuration. Although they have a negligible risk for progression, they are not completely benign and still have a tendency to recur. PUNLMPs are a rare condition that does not require aggressive therapy.

C. Transitional Cell Carcinoma

Approximately 90% of all bladder cancers are TCCs. These tumors most commonly appear as papillary, exophytic lesions; less commonly, they may be sessile or ulcerated. Whereas the former group is usually superficial in nature, sessile growths are often invasive. CIS is recognizable as flat, anaplastic epithelium. The urothelium lacks the normal cellular polarity, and cells contain large, irregular hyperchromatic nuclei with prominent nucleoli.

D. Nontransitional Cell Carcinomas



1. Adenocarcinoma

Adenocarcinomas account for <2% of all bladder cancers. Primary adenocarcinomas of the bladder may be preceded by cystitis and metaplasia. Histologically, adenocarcinomas are mucus secreting and may have glandular, colloid, or signet-ring patterns. Whereas primary adenocarcinomas often arise along the floor of the bladder, adenocarcinomas arising from the urachus occur at the dome. Both tumor types are often localized at the time of diagnosis, but muscle invasion is usually present. Five-year survival is usually <40%, despite aggressive surgical management.

2. Squamous cell carcinoma

Squamous cell carcinoma accounts for between 5% and 10% of all bladder cancers in the United States and is often associated here with a history of chronic infection, vesical calculi, or chronic catheter use. It may also be associated with bilharzial infection owing to *Schistosoma haematobium*. These tumors are often nodular and invasive at the time of diagnosis. Histologically they appear as

poorly differentiated neoplasms composed of polygonal cells with characteristic intercellular bridges. Keratinizing epithelium is present, although often in small amounts.

3. Undifferentiated carcinomas
Undifferentiated bladder carcinomas, which are rare (accounting for <2%), have no mature epithelial elements. Very undifferentiated tumors with neuroendocrine features and small cell carcinomas tend to be aggressive and present with metastases (Choong et al, 2005; Quek et al, 2005).

4. Mixed carcinoma—Mixed carcinomas constitute 4–6% of all bladder cancers and are composed of a combination of transitional, glandular, squamous, or undifferentiated patterns. The most common type comprises transitional and squamous cell elements. Most mixed carcinomas are large and infiltrating at the time of diagnosis.

E. Rare Epithelial and Nonepithelial Cancers
Rare epithelial carcinomas identified in the bladder include villous adenomas, carcinoid tumors, carcinosarcomas, and melanomas. Rare nonepithelial cancers of the urinary bladder include pheochromocytomas, lymphomas, choriocarcinomas, and various mesenchymal tumors (hemangioma, osteogenic sarcoma, and myosarcoma). Cancers in the vicinity such as prostate, cervix, and rectum may involve the bladder by direct extension. Tumor metastases to the bladder usually are from melanoma (most common), lymphoma, stomach, breast, kidney, lung, and liver.

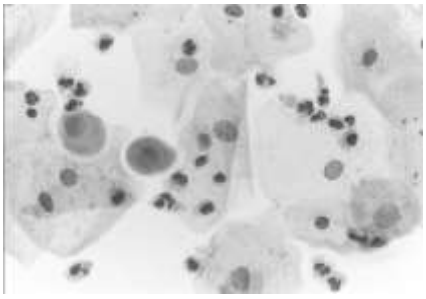
Clinical Findings

A. Symptoms
- Hematuria (painless) is the presenting symptom in 85–90% of patients with bladder cancer. It may be gross or microscopic, more commonly intermittent.
- Symptoms of vesical irritability: frequency, urgency, and dysuria. They are seen in a small subset of patients. Irritative voiding symptoms seem to be more common in patients with diffuse CIS.
- Symptoms of advanced disease include bone pain from bone metastases or flank pain from retroperitoneal metastases or ureteral obstruction.

B. Signs
Patients with large-volume or invasive tumors may be found to have bladder wall thickening or a palpable mass—findings that may be detected on a careful bimanual examination under anesthesia. If the bladder is not mobile, that suggests fixation of tumor to adjacent structures by direct invasion. Hepatomegaly and supraclavicular lymphadenopathy are signs of metastatic disease. Lymphedema from occlusive pelvic lymphadenopathy may be seen occasionally. Patients may also present with back pain or pathologic fracture from bony metastases.

C. Laboratory Findings

1. Routine testing
The most common laboratory finding is hematuria. It may be accompanied by pyuria, which may result from concomitant urinary tract infection. Azotemia may be noted in patients with ureteral occlusion. Anemia may be seen due to chronic blood loss, or replacement of the bone marrow with metastatic disease.



2. Urinary cytology—Exfoliated cells from neoplastic urothelium can be readily identified in voided urine. Larger quantities of cells can be obtained by gently irrigating the bladder with isotonic saline solution through a catheter or cystoscope (barbotage). Detection rates are high for tumors of high grade and stage as well as CIS but not as impressive for low-grade superficial tumors.

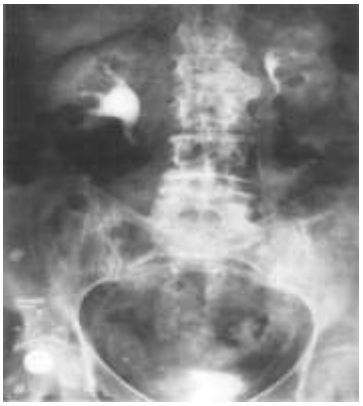
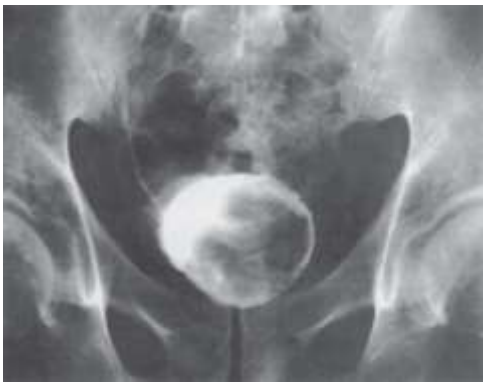
3. Other markers—Several new tests have been developed in order to overcome the shortcomings of urinary cytology such as the low sensitivity for low-grade superficial tumors and inter-observer variability. Commercially available tests include, the bladder tumor antigen (BTA) stat test (Bard Diagnostic Sciences, Inc, Redmond, WA), the BTA TRAK assay (Bard Diagnostic Sciences, Inc), NMP22 assay, and the NMP22 BladderChek test, ImmunoCyt and

UroVysion. Other tests under investigation include identification of the Lewis X antigen on exfoliated urothelial cells, and the determination of telomerase activity in exfoliated cells. These tests have been demonstrated to enhance detection of bladder cancer when used either individually or in combination with cytology. They have been used to detect both new index tumors as well as recurrent tumors. Some of the protein markers lack the specificity of cytology thereby hampering their widespread use.

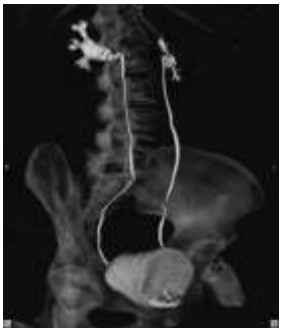
D. Imaging

Although bladder cancers may be detected by various imaging techniques, their presence is confirmed by cystoscopy and biopsy. Imaging is therefore used to evaluate the upper urinary tract and, when infiltrating bladder tumors are detected, to assess the depth of muscle wall infiltration and the presence of regional or distant metastases.

1. Intravenous Urography- Intravenous urography is one of the most common imaging tests for the evaluation of hematuria.

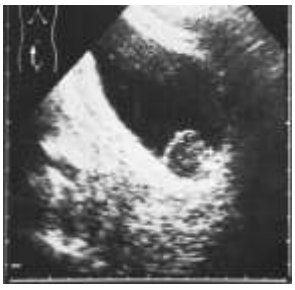



Bladder tumors may be recognized as pedunculated, radiolucent filling defects projecting into the lumen; nonpapillary, infiltrating tumors may result in fixation or flattening of the bladder wall. Hydronephrosis from ureteral obstruction is usually associated with deeply infiltrating lesions and poor outcome after treatment.

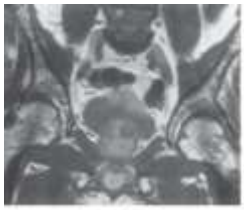
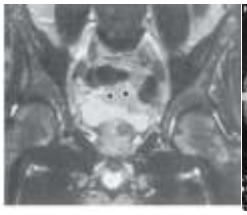
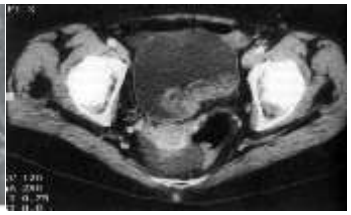


2. Computed Tomography Urography - Computed tomography (CT) urography is used, which is more accurate, for evaluation of the entire abdominal cavity, renal parenchyma, and ureters in patients with hematuria.

3. Ultrasonography – Ultrasonography can primarily detect the presence of bladder tumors as well as comment upon the presence or absence of hydronephrosis.

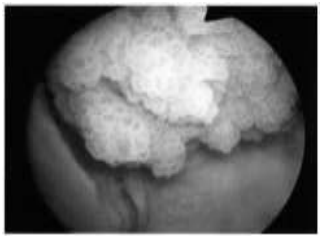


4. Computed Tomography and MRI - Both CT and magnetic resonance imaging (MRI) have been used to characterize the extent of bladder wall invasion and detect enlarged pelvic lymph nodes. Both techniques rely on size criteria for the detection of lymphadenopathy: lymph nodes >1 cm is thought to be suggestive of metastases; unfortunately, small-volume pelvic lymph node metastases are often missed.

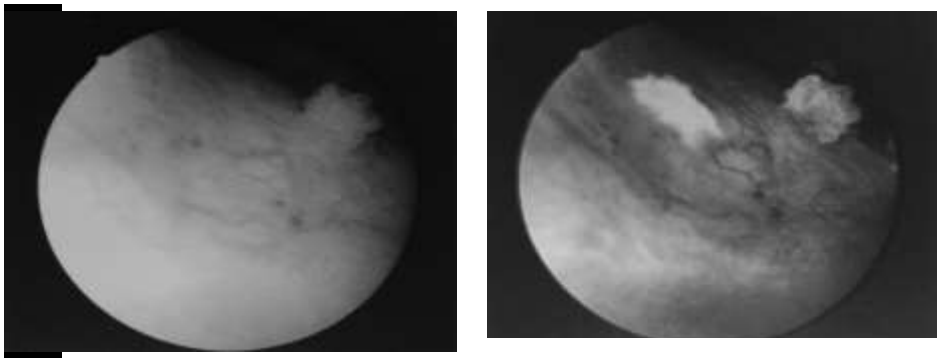
Because invasive bladder cancers may metastasize to the lung or bones, staging of advanced lesions is completed with chest x-ray and radionuclide bone scan. Bone scans can be avoided if the serum alkaline phosphatises is normal. PET scan can also be used to assess metastases from the bladder tumor.

E. Cystourethroscopy and Tumor Resection



The diagnosis of bladder cancer depends on cystoscopic examination of the bladder and histological evaluation of the resected tissue. Cystoscopy can be done with either flexible or rigid instruments, although the former is associated with less discomfort and only requires local anesthesia. Superficial, low-grade tumors usually appear as single or multiple papillary lesions. Higher grade lesions are larger and sessile. CIS may appear as flat areas of erythema and mucosal irregularity.

Use of fluorescent cystoscopy with blue light can enhance the ability to detect lesions by as much as 20%. In this procedure, hematoporphyrin derivatives that accumulate preferentially in cancer cells are instilled into the bladder and fluorescence incited using a blue light. Cancer cells with accumulated porphyria such as 5-aminolevulinic acid or hexaminolevulinate (HAL) are detected as glowing red under the fluorescent light (Loidl et al, 2005). This technology can be particularly useful in the detection of CIS. Using fluorescent cystoscopy may allow for more precise assessment of the completeness of tumor resection, thereby reducing the risk of leaving behind unresected tumor.

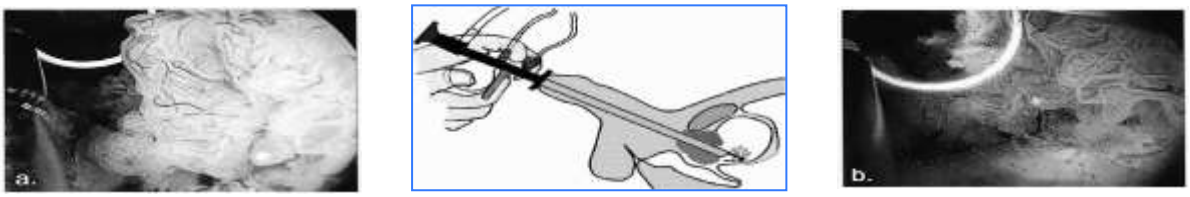


white light cystoscopy

fluorescence-guided cystoscopy

Once a tumor is visualized or suspected, the patient is scheduled for examination under anesthesia and TUR or biopsy of the suspicious lesion. The objectives are tumor diagnosis, assessment of the degree of bladder wall invasion (staging), and complete excision of the low-stage lesions amenable to such treatment. The American Urologic Associations' best practice guidelines for bladder cancer state that as a standard, all patients undergo as complete a resection as possible of all visible tumors (Hall et al, 2007). The presence of any palpable mass and mobility of the bladder are noted along with any degree of fixation to contiguous structures. Cystoscopy is repeated with one or more lenses (30° and 70°) that permit complete visualization of the entire bladder surface. A resectoscope is then placed into the bladder, and visible tumors are removed by electrocautery. Suspicious areas may be biopsied with cup biopsy forceps and the areas may be cauterized with an electrode.

Transurethral resection (TUR)



The goal of TUR is to make the correct diagnosis, which means including **bladder muscle** in the resection biopsies.

Bladder and prostatic urethral biopsy - The biopsies from normal-looking mucosa in patients with bladder tumours so called random biopsies (R-biopsies) or selected site mucosal biopsies are only recommended if fluorescent areas are seen with photodynamic diagnosis (PDD). Cold cup biopsies from normal-looking mucosa should be performed when cytology is positive, when exophytic tumour is of non-papillary appearance, or when fluorescent areasare seen with PDD.

Natural History and Selection of Treatment

Standard Histopathological Assessment

The natural history of bladder cancers is defined by two separate but related processes: tumor recurrence and progression. Progression, including metastasis, represents the greater biologic risk. However, recurrence, even without progression, represents substantial patient morbidity in that it requires periodic re-evaluation (cytology, cystoscopy, etc), repeat endoscopic ablation, and often intravesical chemotherapy (which may be costly, uncomfortable, and associated with complications).

The classic way to categorize patients with **TaT1 tumours** is to divide them into risk groups based on prognostic factors.

The scoring system is based on the six most significant clinical and pathological factors:

- number of tumours
- tumour size
- prior recurrence rate
- T category
- presence of concomitant CIS
- tumour grade

Prognostic factors for NMIBC

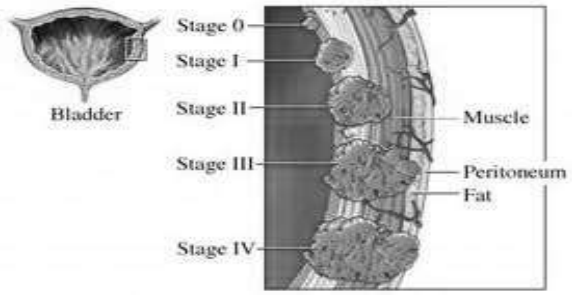
Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2-7	3	3
≥ 8	6	3
Tumour diameter		
< 3 cm	0	0
≥ 3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤ 1 recurrence/year	2	2
> 1 recurrence/year	4	2
Category		
Ta	0	0
T1	1	4
Concomitant CIS		
No	0	0
Yes	1	6
Grade (1973 WHO)		
G1	0	0
G2	1	0
G3	2	5
Total score	0-17	0-23

CIS = carcinoma in *situ*

Probability of **recurrence** and **progression** according to total score

Recurrence score	Probability of recurrence at 1 year %	(95% CI)	Probability of recurrence at 5 years %	(95% CI)	Recurrence risk group
0	15	(10-19)	31	(24-37)	Low risk
1-4	24	(21-26)	46	(42-49)	Intermediate risk
5-9	38	(35-41)	62	(58-65)	
10-17	61	(55-67)	78	(73-84)	High risk
Progression score	**Probability of progression at 1 year %**	**(95% CI)**	**Probability of progression at 5 years %**	**(95% CI)**	**Progression risk group**
0	0.2	(0-0.7)	0.8	(0-1.7)	Low risk
2-6	1	(0.4-1.6)	6	(5-8)	Intermediate risk
7-13	5	(4-7%)	17	(14-20)	High risk
14-23	17	(10-24)	45	(35-55)	

Treatment decisions are based on tumor stage and grade. Staging is performed using the tumor, node, metastasis (TNM) staging system while grading has changed from the Ash-Broder system (I–III or I–IV).



Staging

Stage	TNM		5-y. Survival
0	Ta/Tis	NoMo	>85%
I	T1	NoMo	65-75%
II	T2a-b	NoMo	57%
III	T3a-4a	NoMo	31%
IV	T4b	NoMo	24%

TNM staging and prognosis

The new WHO-ISUP system segregates tumors into papillary urothelial neoplasm of low malignant potential (PUNLMP), low grade or high grade.

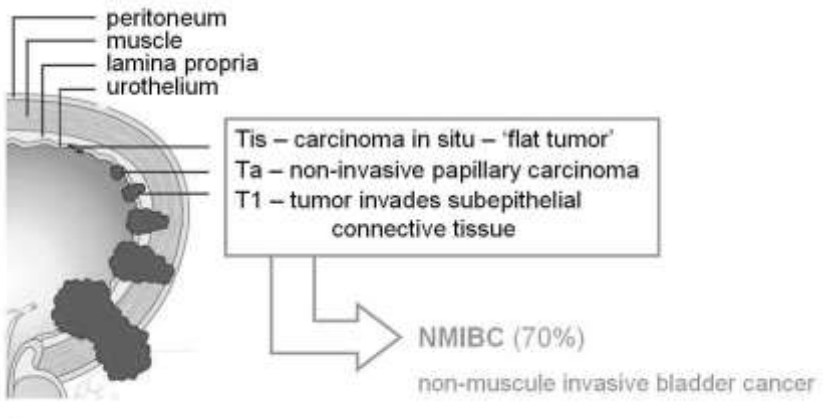
1973 WHO grading

- Urothelial papilloma
- Grade 1: well differentiated
- Grade 2: moderately differentiated
- Grade 3: poorly differentiated

2004 WHO grading

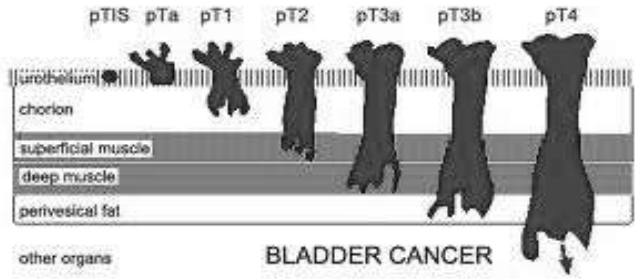
- Urothelial papilloma
- Papillary urothelial neoplasm of low malignant potential (PUNLMP)
- Low-grade papillary urothelial carcinoma
- High-grade papillary urothelial carcinoma

At initial presentation, 74% of bladder tumors are superficial or nonmuscle invasive—stage Tis, Ta, or T1 (David et al, 2009). Invasion into the muscle wall and beyond is identified in a smaller number of patients, approximately 26; regional or distant metastases are found in approximately 25%. Unfortunately, 80% of patients with invasive or metastatic disease have no previous history of bladder cancer (Kaye and Lange, 1982).



About 47% of the tumors are high grade and 53% are low grade at diagnosis (David et al, 2009). A majority of patients with T1 disease can be further sub classified into groups based on the level of lamina propria invasion. The depth of lamina propria invasion is predictive of the likelihood of recurrence and progression (Orsola et al 2005). There are strong correlations between tumor grade and stage and tumor recurrence, progression, and survival (Frazier et al, 1993). Patients with low-stage, low-grade disease have a low risk (<5%) of progression to invasive disease, while as many as 40% of patients with low-stage but high-grade disease will progress with extended follow-up (Herr, 2000).

Pathological Staging



Disease-free survival is excellent for patients with pathologically confirmed superficial disease (pT0, pT1, pTIS, 80–88%). However, it falls for patients with pT2 (53–80%), pT3 (39–68%), and pT4 (25–40%) tumors (Frazier et al, 1993; Stein et al, 2001; Thrasher et al, 1994)—owing to the greater likelihood of metastasis in tumors of higher stage. Although lymph node metastases are uncommon (5%) in tumors of low stage, they are increasingly more common in higher stage tumors: 10–30% for pT3A, 31–46% for pT3B, and 35–64% for pT4 (Frazier et al, 1993; Stein et al, 2001). In patients with organ confined disease, the presence of pelvic lymph node metastases appears to be the most important prognostic factor (Vieweg et al, 1999). The presence of lymphovascular invasion even in those with node-negative disease may portend a worse prognosis (Lotan et al, 2005). Although metastasis is less common with superficial bladder cancers, such tumors may progress; most recur and require additional treatment. Tumor progression occurs in <6% of patients with Ta disease, but in up to 53% of those with T1 disease, with or without concomitant CIS (Cookson et al, 1997; Heney et al, 1983). Tumor progression occurs in 10–20% of patients with grade I tumors, 19–37% with grade II tumors, and 33–64% with grade III tumors (Lutzeyer et al, 1982; Torti et al, 1987). Tumors can be stratified into low-, intermediate- and high-risk categories based on these criteria and this can be used to guide management decisions.

Treatment selection

Patients with superficial bladder cancers can be treated with TUR followed by selective intravesical chemotherapy or immunotherapy. Patients with initial low-grade small tumors are at low risk of progression and may be treated by TUR alone followed by surveillance or intravesical chemotherapy. In some patients with recurrent, low-grade tumors, fulguration of such tumors using electrocautery in an office setting under local anesthesia is also an acceptable alternative.

Patients with T1, high-grade, multiple, large, recurrent tumors or those associated with CIS on bladder biopsies are at a higher risk of progression and recurrence and should be considered candidates for intravesical chemotherapy or immunotherapy after complete and careful TUR.

A second resection of the same area may be required to accurately stage disease and determine treatment. Repeat resections may also enhance response to intravesical therapy (Herr, 2005).

Management of T1 tumors is somewhat controversial; some clinicians advise radical cystectomy, especially for high-grade lesions, which are associated with a high rate of progression. However, progression rates can be reduced by intravesical immunotherapy (Cookson and Sarosdy, 1992; Herr et al, 1989). Recurrence of T1 disease after a trial of intravesical therapy warrants more aggressive therapy such as cystectomy (Herr, 1991; Herr and Sogani, 2001).

Patients with more invasive, but still localized, tumors (T2, T3) are candidates for more aggressive local treatment, including partial or radical cystectomy, or a combination of radiation and systemic chemotherapy. Radical TUR alone may be a viable option in select patients with T2 disease, particularly if no tumor is found on repeat resection since 10-year survival rates as high as 83% can be achieved (Herr, 2001). However, this approach must be used with caution since there is a substantial risk of leaving residual disease behind (Solsona et al, 1998). Superficial ductal or acinar in situ carcinoma of the prostatic urethra, not invading the basement membrane or prostatic stroma, may be treated with TUR and intravesical chemotherapy or immunotherapy rather than cystectomy. However, patients with more extensive involvement of the prostatic urethra by TCC, or recurrence after conservative therapy, require more aggressive therapy. Patients with unresectable local tumors (T4B) are candidates for systemic chemotherapy, followed by surgery (or possibly irradiation). Patients with either local or distant metastases should receive systemic chemotherapy followed by the selective use of either irradiation or surgery, depending on the response.

Cancer stage	Initial treatment options
Tis	Complete TUR followed by intravesical BCG
Ta (single, low-to-moderate grade, not recurrent)	Complete TUR
Ta (large, multiple, high grade, or recurrent)	Complete TUR followed by intravesical chemo- or immunotherapy
T1	Complete TUR followed by intravesical chemo- or immunotherapy or radical cystectomy
T2–T4	Radical cystectomy Neoadjuvant chemotherapy followed by radical cystectomy Radical cystectomy followed by adjuvant chemotherapy Concomitant chemotherapy and irradiation
Any T, N+, M+	Systemic chemotherapy followed by selective surgery or irradiation

Treatment

A. Intravesical Chemotherapy

Immunotherapeutic or chemotherapeutic agents can be instilled into the bladder directly via catheter, thereby avoiding the morbidity of systemic administration in most cases. Intravesical chemotherapy is used in two settings. When instilled immediately following TUR, it acts prophylactically to reduce tumor cell implantation (Solsona et al, 1999). It can also be used therapeutically to reduce risk of recurrence and progression particularly for low-risk superficial tumors.

Most agents are administered weekly for 6 weeks except when being used prophylactically where a single dose is administered immediately following TUR.

Maintenance therapy (ie, monthly or bimonthly intravesical therapy) may decrease recurrence rates further. Although local toxicity is relatively common—primarily irritative voiding symptoms—systemic toxicity is rare. Severe systemic complications can be avoided by not administering intravesical chemotherapy in patients with gross hematuria. Efficacy may be improved by increasing contact time and drug concentration (ie, by restricting fluid intake before administration, asking the patient to lie in different positions during treatment, avoiding instillation of air during drug administration, and requiring the patient to avoid urinating for 1–2 hours thereafter). The most common agents used are mitomycin C, thiotepa, and Bacillus Calmette-Guerin (BCG)

1. Mitomycin C—Mitomycin C is an antitumor, antibiotic, alkylating agent that inhibits DNA synthesis. It has a molecular weight of 329 and systemic absorption is minimal. The usual dose is 40 mg in 40 cc of sterile water or saline given once a week for 6 weeks. The same dose is utilized for a single prophylactic instillation. Side effects are noted in 10–43% of patients and consist largely of irritative

voiding symptoms including urinary frequency, urgency, and dysuria. Unique side effect of this drug is the appearance of a rash on the palms and genitalia in approximately 6% of patients, but this effect can be alleviated if patients wash their hands and genitalia at the time of voiding after intravesical administration. Instillation of Mitomycin C into the bladder immediately post-TUR has been shown to decrease recurrences and prolong the interval to recurrence (Sylvester et al, 2004). Hence it is now considered standard of care to instill one dose of 40 mg of Mitomycin C into the bladder immediately post-TUR to reduce risk of recurrence (Hall et al, 2007).

2. Thiotepa—Thiotepa is an alkylating agent with a molecular weight of 189. 30 mg weekly is an adequate dose. Up to 55% of patients respond completely and have a low recurrence rate. Cystitis after instillation is usually mild and self-limited. Myelosuppression manifested as leukopenia and thrombocytopenia occurs in up to 9% of patients owing to systemic absorption.

3. BCG—BCG is an attenuated strain of Mycobacterium bovis. BCG immunotherapy is used in the treatment of **Ta**, **T1**, and **CIS** urothelial carcinoma of the bladder. Advantages – decrease the rate of recurrence and progression, it is the most effective intravesical therapy. Mechanism of action: Immune response against BCG surface antigens and cross-reacted with putative bladder tumor antigens. BCG has been shown to be very effective both therapeutically and prophylactically. It appears to be the most efficacious intravesical agent for the management of CIS. Complete responses are recorded in 36–71% of patients with residual carcinoma (Catalona and Ratliff, 1990; Herr et al, 1987). Recurrence rates are reduced substantially in patients treated after endoscopic resection (11–27% versus a 70% recurrence after endoscopic resection alone) (Catalona and Ratliff, 1990; Herr et al, 1985; Herr et al, 1987; Lamm, 1985). BCG has been shown to be superior to intravesical chemotherapy in preventing recurrence in patients with high-risk superficial bladder cancer (Lamm et al, 1991). Although BCG appears to be effective in delaying progression of high-risk superficial bladder cancer, 40–50% of these patients will experience disease progression with extended follow-up and many patients will ultimately require cystectomy (Cookson et al, 1997; Davis et al, 2002; Herr et al, 1995). The most commonly recommended induction regimen for BCG is weekly for 6 weeks followed by a period of 6 weeks where no BCG is given. Maintenance therapy should be considered in high-risk patients Maintenance BCG appears to be more effective than intravesical chemotherapy with mitomycin C for intermediate- and high-risk superficial bladder cancer (Bohle, 2003). BCG is more effective than chemotherapy in preventing progression of superficial cancers (Sylvester et al, 2005). Side effects of intravesical BCG administration are relatively common, although severe complications are uncommon. Most patients experience some degree of urinary frequency and urgency. Hemorrhagic cystitis occurs in approximately 7% of patients, and evidence of distant infection is found in <2%. Patients with mild systemic or moderate local symptoms should be treated with isoniazid (300 mg daily) and pyridoxine (vita-min B6 50 mg/day), and the dosage of BCG should be reduced. Isoniazid is continued while symptoms persist and stopped 1 day before the next instillation. Patients with severe systemic symptoms should have instillations stopped. Patients with prolonged high fever (>103°F), symptomatic granulomatous prostatitis, or evidence of systemic infection require treatment with isoniazid and rifampin (600 mg daily). Patients with signs and symptoms of BCG sepsis (eg, high fever, chills, confusion, hypotension, respiratory failure, jaundice) should be treated with isoniazid, rifampin, and ethambutol (1200 mg). The addition of cycloserine (500 mg twice daily) or prednisolone (40 mg daily) increases survival rates (Lamm, 1992).

4. New intravesical agents and approaches—Studies of interferon-alpha and valrubicin (an anthracycline derivative) suggest that these agents, either alone or perhaps in combination with other agents, may be effective in either high-risk patients or those who fail to respond to first-line therapy. Other agents that have been tested in the context of salvage intravesical therapy following BCG failure have been Gemcitabine as well as Docetaxel. Gemcitabine showed promise in an early, phase I study but subsequent studies have not demonstrated similar efficacy in this setting (Dalbagni et al, 2006). Docetaxel also demonstrated a good response in an initial phase I study but subsequent follow-up revealed that the response was not durable unless further induction and maintenance doses were administered (Barlow et al, 2009). Other agents used are Valrubicin, Doxorubicin, epirubucin.

B. Surgery

1. TUR—TUR is the initial form of treatment for all bladder cancers. It allows a reasonably accurate estimate of tumor stage and grade and the need for additional treatment. Patients with single, low-grade, non-invasive tumors may be treated with TUR alone; those with superficial disease but high-

risk features should be treated with TUR followed by selective use of intravesical therapy, as described above. TUR alone has rarely been used in the management of patients with invasive bladder cancer because of a high likelihood of recurrence and progression. Such an approach has been used infrequently for carefully selected patients with comorbid medical conditions and either no residual disease or minimal disease only at restaging TUR of bladder tumor (Herr et al, 1987; Solsona et al, 1998). Careful follow-up of patients with superficial bladder cancers is mandatory because disease will recur in 30–80% of patients, depending on cancer grade, tumor stage, and number of tumors. Disease status at 3 months after initial resection is an important predictor of the risk of subsequent recurrence and progression (Holmang and Johansson, 2002; Solsona et al, 2000). For patients who presented initially with solitary, low-grade lesions and who are free of recurrence at 3 months, repeat cystoscopy at 1 year is suggested. Patients who presented initially with multiple or higher grade lesions (or both) and those who have recurrences at 3 months require more careful surveillance. In such patients, cystoscopy at 3-month intervals is necessary. Although periodic cystoscopy is suggested for all patients with a history of bladder cancer, the risk of recurrence decreases as the tumor-free interval increases.

2. Partial cystectomy— Given current techniques of bladder replacement surgery, partial cystectomy is uncommonly indicated in the management of patients with invasive bladder cancer.

3. Radical cystectomy— The standard treatment for patients with muscle-invasive bladder cancer is radical cystectomy. However, this 'gold standard' only provides 5-year survival in about 50% of patients. Traditionally radical cystectomy is recommended for patients with muscle-invasive bladder cancer T2-T4a, N0-Nx, M0.Other indications include high-risk and recurrent superficial tumours, BCG-resistant Tis, T1G3 and extensive papillary disease that cannot be controlled with TUR and intravesical therapy alone. Salvage cystectomy is indicated for non-responders to conservative therapy, recurrences after bladder sparing treatments, non-urothelial carcinomas and as a purely palliative intervention for e.g. fistula formation, pain or recurrent macrohematuria. Radical cystectomy includes the removal of the bladder, prostate, seminal vesicles, uterus, adnexa and lymphadenectomy (removal of the obturator, internal, external, common iliac, presacral nodes and nodes at the aortic bifurcation). The inclusion of the entire prostate in male patients, and the extent of urethrectomy and vaginal resection in female patients has recently been questioned. Urinary diversion may be accomplished using a variety of techniques. Methods have been developed that allow construction of reservoirs that are continent and do not require the patient to wear an external appliance for collection of urine. From an anatomical standpoint three alternatives are presently used after cystectomy –

- Abdominal diversion such as ureterocutaneostomy, ileal or colonic conduit, and various forms of acutaneous continent pouch
- Urethral diversion which includes various forms of gastrointestinal pouches attached to the urethra as a continent, orthotopic urinary diversion (neobladder, orthotopic bladder substitution)
- Rectosigmoid diversions, such as uretero(ileo-)rectostomy.

7.6 Recommendations

7.6.1 Recommendations for radical cystectomy

- Radical cystectomy in T2-T4a, N0-NX, M0, and high risk non-muscle invasive BC as outlined above (Grade of recommendation: B)
- No preoperative radiotherapy (Grade of recommendation: A)
- Lymph node dissection should be an integral part of cystectomy, extent not established (Grade of recommendation: B)
- Preservation of the urethra is reasonable if margins are negative. If no bladder substitution is attached the urethra must be checked regularly (Grade of recommendation: B)
- Laparoscopic and robot assisted laparoscopic cystectomy may be an option. Current data, however, have not sufficiently proven its advantages or disadvantages (Grade of recommendation: C).

7.6.2 Recommendations for urinary diversion

- Treatment is recommended at centers experienced in major types of diversion techniques and postoperative care (Grade of recommendation: B)
- Before cystectomy, the patient should be counselled adequately regarding all possible alternatives, and the final decision should be based on a consensus between patient and surgeon (Grade of recommendation: B).
- An orthotopic bladder substitute should be offered to male and female patients lacking any contraindications and who have no tumour in the urethra and at the level of urethral dissection (Grade of recommendation: B)

C. Radiotherapy

External beam irradiation (5000–7000 cGy), delivered in fractions over a 5- to 8-week period, is an alternative to radical cystectomy in well-selected patients with deeply infiltrating bladder cancers. Treatment is generally well tolerated, but approximately 15% of patients may have significant bowel, bladder, or rectal complications. Five-year survival rates for stages T2 and T3 disease range from 18% to 41% (Goffinet et al, 1975; Quilty and Duncan, 1986; Woon et al, 1985). Unfortunately, local recurrence is common, occurring in approximately 33–68% of patients. Consequently, radiation as monotherapy is usually offered only to those patients who are poor surgical candidates due to advanced age or significant comorbid medical problems.

D. Chemotherapy

Approximately 15% of patients who present with bladder cancer are found to have regional or distant metastases; approximately 30–40% of patients with invasive disease develop distant metastases despite radical cystectomy or definitive radiotherapy. Without treatment, survival is limited. Early results with single chemotherapeutic agents and, subsequently, combinations of drugs have shown that a significant number of patients with metastatic bladder cancer respond partially or completely (Scher and Sternberg, 1985). The single most active agent is cisplatin, which, when used alone, produces responses in approximately 30% of patients (Yagoda, 1983). Other effective agents include methotrexate, doxorubicin, vinblastine, cyclophosphamide, gemcitabine, and 5-fluorouracil. Response rates improve when active agents are combined. The regimen of methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin (MVAC) has been the most commonly used for patients with advanced bladder cancer (Sternberg et al, 1988; Tannock et al, 1989). Approximately 13–35% of patients receiving such regimens attain a complete response. However, the median survival time is approximately 1 year, and the sustained survival rate is 20–25%. Treatment with MVAC is associated with substantial toxicity, including a toxic death rate of 3–4%. Other newer agents demonstrating activity in this disease include ifosfamide, gemcitabine, paclitaxel, and gallium nitrate (Fagbemi and Stadler, 1998). A study demonstrated similar overall survival, time to treatment failure, and response rate for patients treated with MVAC and those treated with the combination of gemcitabine and cisplatin (von der Maase et al, 2000). The advantage of gemcitabine and cisplatin over MVAC is significantly lower toxicity and improved tolerability.

E. Combination Therapy

Chemotherapy can be given before planned radical cystectomy (neoadjuvant) in an attempt to decrease recurrence rates and, in selected cases, allow for bladder preservation. Approximately 22–43% of patients achieve a complete response to chemotherapy alone (Scher et al, 1988; Scher, 1990). However, additional treatment is still indicated because a substantial number of patients who believed to be free of tumors after chemotherapy alone are found to have infiltrating disease at the time of surgery (Scher et al, 1989). Patients who undergo neoadjuvant chemotherapy are more likely to have no residual tumor in the bladder at cystectomy and this portends a better long-term survival (Grossman et al, 2003). Alternatively, adjuvant chemotherapy may be offered to selected patients after radical cystectomy because of an increased risk of recurrence due to the presence of locally advanced disease (ie, P3, P4, or N+) (Freiha et al, 1996; Logothetis et al, 1988; Scher, 1990; Skinner et al, 1991; Stockle et al, 1992; Stockle et al, 1995). More recently, investigators have treated patients with invasive bladder cancer with complete TUR followed by concomitant chemotherapy and radiation. Cisplatin and Gemcitabine have been the chemotherapeutic agents with the best radio sensitizing activity in these regimens (Oh et al, 2009). Early cystectomy is offered to those who do not tolerate chemotherapy, radiation, or both owing to toxicity and those whose cancers fail to respond to such therapy. Complete response rates to chemo radiation may be as high as 50–70% initially, with 5-year overall survival rates approaching 50–60%. However, local recurrence is common, exceeding 50% in many of these studies. However patients who develop superficial disease recurrence (most commonly CIS) are more likely to require salvage cystectomy with only 34% being alive with a preserved bladder at 8 years compared to 61% of those who do not have such disease recurrence. Owing to invasive local recurrences, only 18– 44% of patients may be alive with an intact bladder 5 years after chemo radiation. Local disease stage and completeness of initial TUR are predictive of response and survival while delivery of radiation therapy by itself is not (Rodel et al, 2002). Predictors of poor outcome after combined chemo radiation for invasive bladder cancer include hydronephrosis at presentation, advanced clinical tumor stage, inability to complete the entire treatment protocol, and poor performance status.

Carcinoma Penis

Sanjay Gupta

Clinical presentation[1]

Penile carcinoma presents most often as a visible or palpable lesion on the penis. The lesion may be an ulcer with raised edge or an area of induration or warty growth. The patient describes the lesion as mass, lump or nodule (47% cases); sore or ulcer (35% cases); and an inflammatory lesion (17% cases).

In an uncircumcised male the patient may complain of recent inability to retract prepuce, foul smelling (and often bloody) discharge from prepuce or a bulge under the prepuce. In some of these patients the primary penile lesion goes unnoticed and the patient presents with inguinal masses. Patients with advanced disease may additionally complain of fatigue, weight loss or bone pains.

Differential diagnosis

A variety of lesions occurring on the penis may mimic penile cancer. Ulcerated lesions of sexually transmitted diseases including primary chancre of syphilis, chancroid, lymphogranuloma venereum and granuloma inguinale may occasionally be mistaken for carcinoma of penis.

Inflammatory lesions of psoriasis, lichen planus, zoon's balanitis, lichen sclerosis etc. have to be differentiated from early, non-ulcerated forms of penile cancer. Genital warts caused by Human Papilloma Virus infection form differential diagnosis of penile cancer, and may indeed be premalignant.

Clinical evaluation

A high index of suspicion should be maintained for men presenting with cutaneous lesions of penis, particularly in those with risk factors for penile cancer. History regarding the duration of lesion, its behavior over time and response to any treatment should also be noted.

Clinical examination of patient with a penile lesion is done to rule out the possibility of a non-malignant disease and the need for biopsy. The presence of a hard, indurated, irregular ulcer or nodule suggests the possibility of penile cancer. Local examination also includes looking for presence of premalignant lesions. Diameter of the penile lesion, site on the penis involved (e.g. foreskin, glans, and shaft), number of lesions, color and morphology (flat, papillary, nodular, ulcerating or fungating) and relationship with other structures (e.g. subepithelial tissue, corpus spongiosum, corpora cavernosa, urethra) should be evaluated. The length of uninvolved shaft should be noted, as the choice of partial amputation of penis depends on this.

Inguinal and iliac regions should be examined for presence of lymph nodes, their number, size and fixity. Presence of urinary obstruction and lower extremity edema should be noted, as these suggest advanced local and nodal disease. A thorough systemic examination should also be done for any skin lesions elsewhere in the body, presence of coexisting disease and evidence of metastasis.

Biopsy[2]

Confirming the diagnosis of penile cancer is by histological or cytological examination. Tissue sampling options include:

- incisional biopsy
- tissue core biopsy
- fine-needle aspiration
- brush biopsy
- excision biopsy (therapeutic in some cases)

Under local anesthesia, suspicious neoplastic lesions should be biopsied. Specimens can be removed by shaving, or alternatively by punch biopsy using a 2 or 3 mm instrument, or by simple elliptical excision. The latter technique allows either the partial removal (i.e., incisional biopsy) or complete removal (i.e., excisional biopsy) of a lesion. Shaving biopsy is usually not recommended.

Biopsy should always be deep, as small or superficial penile biopsies are difficult to classify with regard to histological type, grade, invasion and other pathologic parameters related to prognosis. Pathological diagnosis is especially difficult in cases of verruciform and mixed carcinoma. Quite often the final grade based on penectomy specimen is higher than that based on initial biopsy.

Imaging[3]

While clinical examination of penile cancer gives a fairly accurate idea about the local stage of the disease, the depth of the lesion is difficult to assess accurately. Presence of non-malignant penile edema tends to overestimate the local stage. Imaging of primary lesion, lymph nodes as well as distant metastatic sites are needed for accurate staging of penile cancer.

Imaging of primary tumor

While both ultrasonography and MRI scanning are useful, CT scan does not have adequate contrast and spatial resolution to be of any benefit. Artificial erection, induced by 5-20 microgram of intracavernosal prostaglandin E1, improves the staging accuracy by stretching the tunica albuginea, making defects or invasion easier to see, and it increases contrast between tumor and corpora. Contraindications should be kept in mind when inducing artificial erection.

Imaging improves the accuracy of detecting corporal involvement, thus helping to differentiate T1 from T2 lesions. It also helps to differentiate cavernosa from spongiosum involvement. This is important as cavernosal involvement has poorer prognosis than spongiosum involvement.

As per EAU guidelines MRI is more accurate than ultrasonography for larger tumors with deep invasion; in smaller tumors ultrasound may be of higher resolution, though, if the tumor is small and superficial, imaging may not add usefully to clinical and operative findings.

Assessing Lymph Nodes and Distant Metastases

Malignant lymph nodes are identified on imaging by presence of focal necrosis, loss of fatty hilum and change of shape from oval to round. Imaging is useful in low and intermediate risk disease with non-palpable lymph nodes. CT of pelvis and abdomen is indicated in all node positive disease, with bone scan in symptomatic patients. Imaging also plays an important role in follow up of treated patients.

Staging[4]

The anatomic extent of the primary tumor plays an important role in clinical decision making with respect to management of the primary tumor and the likelihood of inguinal lymph node metastasis. Superficial tumors are often managed using organ preserving strategies whereas more advanced tumors often require amputative approaches. However, lymphovascular invasion even in the presence of superficial lesion carries worse prognosis and needs more aggressive treatment.

Inguinal region should be clinically evaluated for enlarged lymph nodes. Computed tomography and MRI are useful adjuncts in patients in whom palpation is unreliable (i.e., obese, prior inguinal surgery or radiotherapy).

Beyond management of the primary tumor, clinicians must decide if the inguinal region is at risk for metastases from the primary tumor, as the incidence and extent of metastases are the most important factors determining survival. Patients with no nodal metastases exhibit the best disease free survival. Inguinal lymph node metastasis is managed by lymphadenectomy while those with extranodal extension of cancer and pelvic lymph node metastases are rarely cured with surgery alone.

Thus, clinical and pathologic staging information not only determines prognosis but forms the basis of integrating systemic chemotherapy or radiation into the treatment regimen for select patients with more advanced disease.

Treatment[5]

The appropriate treatment of penile cancer is based on the stage and grade of the disease. The need to preserve the sexual function, the likelihood of patient remaining under regular follow up and the

availability of specialized surgical and radiotherapy techniques also influence the final treatment choice.

Management of primary lesion
For patients with *in situ* or non-invasive verrucous carcinoma, penis preserving techniques may be used. The treatment options include:

- topical imiquimod (5%) or 5-FU cream
- circumcision, if localized to prepuce
- wide local excision (Mohs surgery, frozen section controlled excision)
- laser ablation
- glansectomy

For low grade tumor limited to subepithelial tissue, penis preserving therapy in suitable patients may be considered. This may be in the form of wide local excision, laser therapy or radiotherapy. Options for radiotherapy include external beam radiotherapy (ERBT) or brachytherapy.

On the other hand, for high grade tumor limited to subepithelial tissue, in addition to above, partial/ total penectomy (depending upon the size and location of the lesion) or radiotherapy in combination with chemotherapy may be needed.

For tumors infiltrating into corpora (especially cavernosa) wide local excision is not adequate and partial/ total penectomy should be done. Intra-operative frozen section is recommended to achieve negative surgical margins. Radiotherapy alone or in combination with chemotherapy may be considered in suitable cases if preservation of sexual function is desired or if the primary tumor is initially unresectable.

Management of regional lymph nodes
The presence and extent of lymph node involvement is the single most important prognostic indicator of long term survival. The evaluation of inguinal lymph node is done clinically and supplemented by CT scan or MRI (in case of obese patients or those with previous groin surgery or radiotherapy). Number, size, fixity and involvement of one or both inguinal regions are assessed.
Based on the presence of certain risk factors of the primary lesion the likelihood of lymph node metastasis can be predicted. These high risk features include:

- lymphovascular invasion
- poor pathological grade
- poor differentiation in over half of tumor cells

Management of non-palpable lymph nodes
For low risk primary tumors, inguinal lymph nodes should be kept under observation after appropriate treatment of the primary lesion. For high risk primary tumors, inguinal lymphadenectomy should be done. Dynamic sentinel lymph node biopsy is an option for management of these cases.

Management of <4 cm lymph nodes
For unilateral <4 cm inguinal lymph node and low risk primary disease, FNAC followed by inguinal lymph node dissection is the treatment of choice (for positive FNAC). Negative FNAC should be followed by Trucut or excision biopsy of the enlarged node. If the nodes are negative for tumor, the patient may be kept under surveillance.

For patients with high risk primary disease, FNAC may be omitted and the patient directly subjected to inguinal lymph node dissection.

Management of >4 cm lymph nodes
For patients with large mobile/ fixed, unilateral/ bilateral lymph nodes neoadjuvant chemotherapy is given. Radiotherapy may be added if the lymph nodes remain fixed after chemotherapy. Subsequently, the patients undergo inguinal lymph node dissection. If viable cells are detected in lymph node specimen, pelvic lymphadenectomy is added.

Follow up

Patients should be kept under surveillance following the primary treatment of penile cancer and lymph nodes. Patients with penis preserving treatment of primary lesion need closer follow up as these patients have much higher recurrence rates. While clinical examination is usually sufficient, imaging

may be used in case of obese individuals or those where clinical examination of groin is unsatisfactory due to scarring following prior therapy.

Management of recurrence

Local recurrence following previous penis sparing treatment should be followed by partial or total penectomy, especially if the recurrence involves cavernosa. For very select cases, repeat penis sparing procedure may be considered.

For recurrent inguinal disease, surgery/ chemotherapy/ radiotherapy/ combination therapy may be considered though the prognosis remains poor.

Metastatic disease is treated by chemotherapy. Surgery or radiotherapy is considered only for palliation of local symptoms.

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Management of Non Seminomatous Germ Cell Tumour

Rishi Nayyar, Raman Tanwar

Non seminomatous germ cell tumors consist of embryonal carcinoma, yolk sac tumor, choriocarcinoma, teratomas or the mixture of these neoplasms. To manage these tumors it is necessary to have thorough understanding of their behaviour and characteristics.

Embryonal carcinoma is an aggressive tumor with high rates of metastasis. It is the most undifferentiated of all NSGCTs and can mature into other forms of NSGCT. This tumor secretes both AFP and HCG and stains for AE1, AE3 and PLAP. The presence of this tumor and its share in the total tumor is of significance in Stage I NSGCT as it guides prognosis and treatment.

Yolk Sac Tumor often occurs as a part of mixed NSGCTs and pure yolk sac is rarely encountered. These tumors produce AFP. These tumors exhibit hyaline globules and Schiller Duval Bodies. Presence of these tumors is associated with a lower risk of relapse.

Teratomas range from well differentiated to poorly differentiated tumors. They may show mild elevations of AFP. Embryonal tumors may transform to teratomas and proliferate at metastatic sites. Since teratomas are chemotherapy resistant, it is essential to resect them surgically. Teratomas are histologically benign but they may occasionally turn malignant and become highly aggressive and chemoresistant.

Choriocarcinoma is relatively rare and aggressive NSGCT. Usually the disease presents as a metastatic disease spreading through the hematogenous route. It is usually strongly positive for HCG. A hard painless mass in the scrotum is often the presenting sysmptom. It is usually pain free unless the growth is too rapid or there is associated haemorrhage or infarction, and there is little on examination that can suggest non seminomatous over seminomatous tumor. Non seminomatous tumors are more vascular and grow rapidly, making it more probable for them to be painful. In approximately 20% of cases the first symptom is scrotal pain and up to 27% of patients with testicular cancer may have local pain.[1] Important differentials are other scrotal masses like hydrocele, hematocele and chronic epididymo-orchitis.

On examination it is important to look for an abdominal mass as retroperitoneal lymphadenopathy and metastasis may be present in upto 60% of these tumors. Supraclavicular lymphnodes may be involved in some cases. Altered hormonal milieu may result in gynaecomastia (7% of NSGCTs[2]) and decreased fertility. Secondary hydrocele and inguinal lymphadenopathy may also be found.

Ultrasonography is helpful in ruling out the other differentials, ascertain presence of hydrocele, look at the contralateral testis for presence of tumor (2% GCTs are bilateral) and occasionally to rule out a burnt primary tumor. It is advocated for all cases of testicular tumors as sensitivity in detecting a testicular tumour is almost 100%, and it has an important role in determining whether a mass is intra- or extratesticular.[3] Ultrasound is also indicated in follow up of the contralateral testis.[4] MRI of the scrotum may be useful in differentiating seminomatous from non seminomatous lesions.[5]

LDH, AFP and hCG are recommended in every case of suspected testicular cancer (Table 1). Pre Orchiectomy levels are essential. Upto 50% of tumors have been found to be associated with raised markers like LDH.[6] PLAP is an optional marker for testicular tumors.

Marker	***Half Life***	***Testicular Tumour***	***Other Differentials***
LDH	24 hours	All GCTs (20% of low grade and up to 60% of high grade)	Diseases of smooth, cardiac and skeletal muscles, Haemolytic syndromes
AFP	5-7 days	50-70% Low grade NSGCT 60-80% Advanced NSGCTs (Embryonal and Yolk Sac)	Stomach, liver, pancreatic, biliary and lung cancer, benign liver conditions and infections
hCG	24-36 hours	20-40% low stage NSGCTs 20-60% advanced NSGCTs (Embryonal and Choriocarcinoma) 15% of Seminomas	Liver, Biliary, stomach, pancreatic, lung, breast, kidney cancer

High Inguinal orchiectomy is the recommended initial therapy. In synchronous bilateral testicular tumours, metachronous contralateral tumours or in a tumour in a solitary testis with normal pre-operative testosterone levels, organ preserving surgery can be performed if tumour volume is less than 30% of testicular volume.

Staging and Stage-wise Management

The initial aims of diagnosis and workup are to establish a baseline level of markers, and metastatic status into lungs, brain, bones and nodes. Abdominopelvic CT is the investigation of choice to evaluate suspicious retroperitoneal nodes. In cases of doubt an MRI of the abdomen may be useful. A chest CT is mandatory in all patients with NSGCT as upto 10% may harbour metastasis.[7] There is no role of CT of the head in initial workup except for cases with highly elevated hCG (>10,000 IU/L)

TNM classification for testicular cancer (UICC, 2002, 6th edition)

pT Primary tumour[1]
pTX Primary tumour cannot be assessed (see 1, T-Primary tumour)
pT0 No evidence of primary tumour (e.g. histological scar in testis)
pTis Intratubular germ cell neoplasia (carcinoma in situ)
pT1 Tumour limited to testis and epididymis without vascular/lymphatic invasion: tumour may invade tunica albuginea but not tunica vaginalis
pT2 Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis
pT3 Tumour invades spermatic cord with or without vascular/lymphatic invasion
pT4 Tumour invades scrotum with or without vascular/lymphatic invasion

N Regional Lymph Nodes clinical
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension

N2 Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension,
or multiple lymph nodes, any one mass more than 2 cm but not more than 5 cm in greatest dimension
N3 Metastasis with a lymph node mass more than 5 cm in greatest dimension

pN Pathological
pNX Regional lymph nodes cannot be assessed
pN0 No regional lymph node metastasis
pN1 Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension
pN2 Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension;
or more than 5 nodes positive, none more than 5 cm; or evidence or extranodal extension of tumour
pN3 Metastasis with a lymph node mass more than 5 cm in greatest dimension

M Distant Metastasis
MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
M1a Non-regional lymph node(s) or lung
M1b Other sites

S Serum Tumour Markers
Sx Serum marker studies not available or not performed
S0 Serum marker study levels within normal limits

	LDH (U/l)	**hCG (mIU/ml)**	**AFP (ng/ml)**
S1	< 1.5 x N	< 5,000	< 1,000
S2	1.5-10 x N	5,000-50,000	1,000-10,000
S3	> 10 x N	> 50,000	> 10,000

IGCCN Risk Classification for advanced GCT

Good Risk Group
• Testis/retroperitoneal primary • No non-pulmonary visceral metastases • AFP < 1,000 ng/mL • hCG < 5,000 IU/L (1,000 ng/mL) • LDH < 1.5 x ULN
Intermediate Risk Group
• Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Poor Risk Group
• Testis/retroperitoneal primary • No non-pulmonary visceral metastases • AFP > 1,000 and < 10,000 ng/mL or • hCG > 5,000 and < 50,000 IU/L or • LDH > 1.5 and < 10 x ULN

Radical/ High Inguinal Orchiectomy

Every patient is initially subjected to inguinal exploration and orchiectomy with division of the cord at the level of the internal inguinal ring. Only in life-threatening conditions may up-front chemotherapy be started and orchiectomy delayed for later.

It is recommended that sperm preservation be offered to all patients prior to orchiectomy with potential for future families as virtually all patients develop azoospermia after chemotherapy.[8] The recovery of fertility may take 2-5 years after chemotherapy or radiation. Similarly surgery in the form

of Retroperitoneal Lymph node dissection may lead to ejaculatory dysfunction in upto 80% of the patients.

Stage I NSGCT

Surveillance, RPLND and chemotherapy are all viable options in the management of early stage NSGCT. If put on surveillance, upto 30% of patients experience relapse.[9] Upto 80% of these relapses occurs within the first year and despite surveillance upto 10% of patients present with large volume recurrent disease.[10] Lymphovascular invasion has been found to be the important risk factor for occult metastasis from amongst advanced pathological T stage, predominant embryonal carcinoma, absence of yolk sac tumor, MIB-1 staining, patient age and tumor size. The rate of occult metastasis with lymphovascular invasion is 45-90% and that with predominant embryonal component is 30-80%. If these risk factors are absent the risk of occult metastasis is less than 20%.

Chemotherapy with bleomycin, etoposide and cisplatin (PEB) as primary treatment for high-risk patients is an attractive and reliable option. Relapse rates of well below 3% have been reported with minimal toxicity in a large series,[11] but these relapses are more difficult to treat with subsequent surgery. There is minimal impact on the quality of life and fertility. The cost effectiveness is not essentially clear and there is a risk of late chemoresistant relapse with slow growing teratomas which needs to be kept in mind.[12] Overall chemotherapy is the single best modality that can be administered in any setting, however it requires surveillance and has the risk of long term toxicity.

RPLND is the other treatment possibility for clinical stage I NSGCT. Since most relapses and metastasis are retroperitoneal and the procedure offers an almost complete cure it should be offered to the patient at high volume centers. In more than 75% patients chemotherapy can be avoided and even if relapse occurs, the salvage rates with chemotherapy are high. Since upto 25% of the patients have teratoma in the metastasis RPLND offers the best chance of cure. If RPLND is offered to these patients upto 30% may be found to have lymph node metastasis that corresponds to pathological stage II disease.[13] If the nodes turn out to be negative, 10% of these patients are still found to relapse at distant sites.[14] Risk of retroperitoneal relapse after a properly performed nerve-sparing RPLND is very low (less than 2%) and the follow up is much less costlier.[15] If a relapse occurs, it is generally in the chest, neck or at the margins of the surgical field. Pulmonary relapses occur in 10-12% of patients and more than 90% of those relapses occur within 2 years of RPLND.

Patients without vascular invasion constitute about 50-70% of the CS1 population, and these patients have only a 15-20% risk of relapse on surveillance, compared with a 50% relapse rate in patients with vascular invasion.

As a part of risk adapted treatment patients with vascular invasion are recommended to undergo adjuvant chemotherapy with two cycles of BEP and those without vascular invasion may be put on surveillance. These patients may still have to follow with Abdominal CT as the risk of relapse in retroperitoneum is unclear. One course of adjuvant PEB is superior to RPLND with regard to recurrence rates in patients unstratified for risk factors.[16]

Management of Clinical stage 1S tumors

Post orchiectomy markers are followed up closely. Markers that rise or do not fall after orchiectomy are suggestive of residual disease. In these patients nearly 90% are pathologically positive nodes on RPLND. These patients are managed with induction chemotherapy on similar lines as those with Clinical stage IIC or III disease.

Stage II NSGCT

The management of Stage II and beyond non seminomatous tumours depends upon the histological characteristics and the prognostic grades as defined by the IGCCCG.[17] The acceptable treatments include RPLND with or without adjuvant chemotherapy or induction chemotherapy with post chemo RPLND(PCS RPLND). Stage IIA/IIB tumour without elevated markers can be treated with initial chemotherapy, primary RPLND or surveillance. Based on the extent of the disease combination of Cisplatin-based chemotherapy and surgery (aggressive multimodality) achieves cure rates between 65% and 85%.[18] Tumours that are associated with elevated markers should be managed with

chemotherapy (three or four cycles of BEP). Alternatively RPLND with Adjuvant chemotherapy may be offered to these patients where risk is teratoma is high and chance of systemic involvement is low. However high tumor markers postorchiectomy or retroperitoneal lymphadenopathy greater than 3 cm have been correlated with increased risk of systemic relapse after RPLND.

Why RPLND	**Why not RPLND**
• 15-35% patients have no disease and avoid chemotherapy • Ejaculatory function is preserved in 70-90% • 30% have chemoresistant Teratoma	• Additional therapy in upto 50% patients • Upto 15% have persistant disease and require full induction chemotherapy Not possible at all institutions
Why give induction Chemotherapy	**Why avoid Induction Chemo**
• Upto 80% have a complete response • 95-100% cancer specific survival • Available at all institutes	• Long term toxicity • Risk of relapse with chemo-refractory GCT

The BEP Regimen consists of Cisplatin 20 mg/m2, days 1-5, Etoposide 100 mg/m2, days 1-5, and Bleomycin 30 mg administered on days 1,8,15. If Bleomycin is contraindicated due to some reason four cycles of EP may be administered. Alternatively VIP may be substituted for BEP in poor risk patients with pulmonary compromise or thoracic surgery. 3 cycles are given in good prognosis patients, while patients with intermediate prognosis include 4 cycles of BEP.[19] 5 year survival in this group is about 80%. Patients with poor risk are also served best with 4 cycles of BEP chemotherapy, but 5 year progression free survival is in the order of 45-50%. These patients may be enrolled in ongoing prospective trials for high dose chemotherapy. Management should be done preferably at a referral center.

Stage IIC and III NSGCT

The initial therapy recommended in these patients is induction chemotherapy. 4 cycles of BEP is the standard regimen.

Once complete remission is achieved with chemotherapy, surgery is not indicated. Such a scenario arises in 25-60% of patients. If any residual mass is left (30% of cases), it should be removed preferably using nerve sparing RPLND within 4-6 weeks of chemotherapy (PCS).[20] In these specimens only 10% have viable cancer, while 50% contain mature teratoma and 40% contain fibrosis and necrotic tissue. Absence of teratoma in the primary tumor and good response to chemotherapy are useful predictors of necrosis in the PCS specimen. A complete resection of all visible masses is critical.[21] If the resected specimen shows presence of mature teratoma or necrosis, no further therapy is instituted. In case of incomplete resection of teratoma or vital tumor, two cycles of adjuvant cisplatin based chemotherapy is beneficial. Unresected teratoma may grow rapidly (growing teratoma syndrome) and undergo malignant change.

Follow up Protocol for surveillance of stage I NSGCT

Procedure	**Year 1**	**2**	**3–5**	**6–10**
Physical examination	3-monthly	3-monthly	Twice/year	Once/year
Tumour markers	3-monthly	3-monthly	Twice/year	Once/year
Chest X-ray	Twice/year	Twice/year		
Abdominopelvic CT scan	Twice/year (at 3 and 12 months)			

Follow up Protocol for RPNLD of stage I NSGCT

Procedure	**Year 1**	**2**	**3–5**	**6–10**
Physical examination	3-monthly	3-monthly	Twice/year	Once/year
Tumour markers	3-monthly	3-monthly	Twice/year	Once/year
Chest X-ray	Twice/year	Twice/year		
Abdominopelvic CT scan	Once/year	Once/year		

Follow up protocol for advanced NSGCT

Procedure	Year 1	2	3–5	6–10
Physical examination	3-monthly	3-monthly	Twice/year	Once/year
Tumour markers	3-monthly	3-monthly	Twice/year	Once/year
Chest X-ray	3-monthly	3-monthly	Twice/year	Once/year
Abdominopelvic CT scan	Twice/year	Twice/year	Once/year	Once/year
Chest CT and Brain CT	As Indicated			

Management of recurrence/ relapse

For recurrent disease or relapse, induction chemotherapy is the treatment of choice using agents like VIP, VeIP or TIP. Long term remission may be achieved in upto 40% of patients. These patients have bulky retroperitoneal lymphadenopathy, elevated markers and occasional distant metastasis. In the absence of these features RPNLD may be offered as the first line treatment.

Prognostic indicators of response to salvage therapy include Location and histology of the primary tumour, Response to first-line treatment, Duration of remissions, Level of AFP and hCG at relapse.10% improvement in survival is noted with the use of high dose chemotherapy but this benefit is doubtful.[22] After chemotherapy surgery should be performed in 4-6 weeks after markers have declined.[23] If the markers do not decline resection of residual tumours ('desperation surgery') should be considered if complete resection of all tumour seems feasible.[24]

Late relapse is defined as any patient relapsing more than 2 years following chemotherapy for metastatic disease. These patients should be subjected to radical surgery as early as possible[25]. Late relapse may be due to viable malignancy (most commonly Yolk Sac tumor), Teratoma (20-30%) or malignant transformation to adenocarcinoma (10-20%). History of prior relapse and teratoma in PCS specimen are predictors of late relapse. Surgical excision of all tumor gives the best cure as late relapses are usually chemoresistant. If there is residual disease following surgery salvage chemotherapy should be started based on histological results. These cases should be managed at high volume centres and surgery should be done once response to chemotherapy has been achieved[26].

Guidelines for the Treatment of NSGCT Stage I

CS 1: Risk-adapted treatments based on vascular invasion or surveillance are recommended treatment options (Grade of recommendation: B)

CS1A (pT1, no vascular invasion): low risk

1. If the patient is willing and able to comply with a surveillance policy and long-term (at least 5 years) close follow-up should be recommended (Grade of recommendation: B).
2. Adjuvant chemotherapy or nerve-sparing RPLND in low-risk patients remain options for those not willing to undergo surveillance. If RPLND reveals PN+ (nodal involvement) disease, chemotherapy with two courses of PEB should be considered (Grade of recommendation: A).

CS1B (pT2-pT4); high risk

Primary chemotherapy with two courses of PEB should be recommended (Grade of recommendation: B). Surveillance or nerve-sparing RPLND in high-risk patients remain options for those not willing to undergo adjuvant chemotherapy. If pathological stage II is revealed at RPLND, further chemotherapy should be considered (Grade of recommendation: A).

Guidelines for the Treatment of Metastatic Germ Cell Tumours

- Low volume NSGCT stage IIA/B with elevated markers should be treated like 'good or intermediate prognosis' advanced NSGCT with 3 or 4 cycles of PEB. Stage II A/B without marker elevation can be treated either by RPLND or close surveillance.
- In metastatic NSGCT (> stage IIC) with a good prognosis, three courses of PEB is the primary treatment of choice (Grade of recommendation: A).
- In metastatic NSGCT with an intermediate or poor prognosis, the primary treatment of choice is four courses of standard PEB (Grade of recommendation: A).

- Surgical resection of residual masses after chemotherapy in NSGCT is indicated in the case of visible residual masses and when serum levels of tumour markers are normal or normalizing (Grade of recommendation: B).
- Metastatic seminoma with less than N3M1 disease can be treated initially with radiotherapy. When necessary, chemotherapy can be used as a salvage treatment with the same schedule as for the corresponding prognostic groups of NSGCT (Grade of recommendation: A).
- Advanced seminoma (N3 or M1) should be treated with primary chemotherapy according to the same principles used for NSGCT (Grade of recommendation: A).

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Investigations for Peripheral Vascular Disease

Anjali Prakash

Evaluation of the Peripheral Arterial System

Peripheral arterial disease is usually secondary to stenotic or occlusive atherosclerosis. The majority of symptomatic patients have intermittent claudication and only a minority (<2% and typically those with diabetes mellitus or renal failure) progress to critical limb ischaemia, heralded by the onset of rest pain and/or loss. Imaging is largely reserved for patients with disabling symptoms in whom revascularisation is planned. In these patients, accurate depiction of the vascular anatomy is critical for clinical decision making as the distribution and severity of disease are key factors determining whether revascularisation should be by endovascular techniques or open surgery. Non-invasive vascular imaging has recently undergone significant refinement and has replaced conventional digital subtraction angiography for many clinical indications.

Radiological Evaluation

Radiological evaluation of Peripheral arterial disease is aimed at providing the following information.

- Presence or absence of significant obstruction to flow.
- Site and anatomical extent of obstruction.
- Condition of collateral flow and distal vasculature for planning treatment.
- Results of therapy and disease progression.

Imaging Modalities

Ultrasound and Doppler Scanning

The arteries of the upper and lower extremities are easily accessible to sonographic imaging with high resolution transducers. Duplex Doppler (the term duplex refers to the combination of B mode and colour Doppler ultrasound) is typically the initial imaging modality of choice. It is widely available and requires no exposure to either ionising radiation or potentially toxic intravascular contrast agent. It is highly portable and in the emergency setting permits a rapid targeted examination.. It can also provide detailed haemodynamic information;

Power Doppler depicts very slow flow, improves visualisation of vascular borders and contours and in cases of stenosis it improves delineation of residual lumen

Flow Patterns on Spectral Doppler

The normal spectral Doppler pattern of arterial flow in the extremities is a high resistance wave form. It consists of a narrow sharply defined tracing indicating that all blood cells are moving at an equivalent speed at any time in the cardiac cycle. The configuration of this wave form is typically triphasic indicating strong forward component of blood flow during systole, followed by a short reversal of flow during diastole. A return to forward flow of lower amplitude normally follows and lasts for a variable length of diastole. The diastolic portion of blood flow is extremely variable disappearing with vasoconstriction due to cold or increasing with warmth or exercise. The diastolic flow is absent in vessels that have lost compliance as in atherosclerosis and diabetes.

Once an abnormal flow pattern is detected by color Doppler, pulsed Doppler spectral sampling is done to better characterise the lesion.

Focal peripheral arterial stenosis is categorised as mild, moderate or severe.

1. With mild stenosis (1-19% luminal diameter reduction) the spectral Doppler tracing reveals mild spectral broadening but waveform maintains its triphasic appearance. PSV is upto 30 per cent greater than the velocity of the normal proximal segment

2. With moderate stenosis (20% to 49% diameter reduction), the waveform remains triphasic but has increased spectral broadening. Doppler tracing demonstrates an increase in PSV that is upto 100 per cent greater than the proximally sampled segment with a velocity ratio 1.5:2.

3. A severe stenosis represents a 50 per cent or greater luminal diameter reduction. This lesion is considered haemodynamically significant as it results in decreased blood pressure and blood flow across the stenosis. There is marked spectral broadening and the waveform at the level of stenosis is monophasic with a PSV that is more thandouble the velocity measured in the proximal segment, i.e. a velocity ratio > 2. In addition because of the pressure drop across the stenosis, the waveform loses its normal diastolic reverse flow component1. This is a significant feature of critical stenosis, and defines a pressure reducing lesion PSV ratios of > 4 correspond to a greater than 80 per cent stenosis and ratios >7 correspond to > 90 per cent stenosis respectively.An occlusion is characterized by absence of flow within an arterial segment.

Ratios of PSV are superior to absolute PSV measurement for classification of peripheral arterial stenosis. In the absence of collaterals high resistance waveform is identified proximal to the occlusion/high grade stenosis. Distal to a significant stenosis/occlusion the waveform shows a typical low resistance pattern due to opening up of collaterals and loss of normal arteriolar tone. There is also a characteristic tardus – parvus waveform in the distal vessel.

The iliac arteries and the vessels of thecalf however are difficult to evaluate in any patients. Evaluation of the superficial femoral in the adductor canal may also be difficult. In the upper limb the origins of brachiocephalic/subclavian arteries are difficult to evaluate. Besides Doppler is a very operator dependent and time consuming procedure and extensive vessel calcification may prevent insonation of stenosis. Further, when an artery is occluded assessment of distal circulation and collaterals is rarely possible.

CT Angiography (CTA)

CTA is a noninvasive means of evaluating blood vessels requiring only an IV injection of contrast. The images can be evaluated in 2D as well as 3DThe advent of multi detector row CT has had substantial impact on CT angiography offering shorter acquisition times, lower doses of contrast medium, increased volumetric coverage and/ or improved Z axis resolution. The introduction of 64 and recently 128 slice CT scanners has further reduced examination times, while increasing volumetric coverage and improving resolution to the tune of 0.24 mm voxel size. The main post processing techniques used are; volume rendering, multiplanar and maximum intensity projections (MIP's). Dual energy CTA is a promising new approach for bone and calcium removal

Advantages of CTA over DSA include 3 D- volumetric data analysis and display, smaller volumes of contrast material, minimal invasiveness and thus a lower complication rate, better visualization of distal arteries and shorter examination times. The peripheral venous rather than central aortic administration of contrast material as is done in DSA allows better opacification of collateral circulation and thus of arteries distal to an occlusion site. CTA unlike sonography is relatively investigator independent and can also assess aspects external to the vessel lumen, not assessed by DSA, including mural thrombus, atheroma, inflammation and periarterial tissues.

In the evaluation of peripheral vascular occlusive disease CTA can be used for characterisation of inflow and run off vessels, as an aid to therapeutic planning and the post operative evaluation after angioplasty or bypass procedures. CTA can be invaluable for planning stent deployment and evaluation of post procedure complications in iliac arteries. Results of recent studies suggest that the use of MD-CTA instead of DSA as the initial diagnostic imaging test for Peripheral arterial occlusive disease provides sufficient information for therapeutic decision making and reduces imaging costs **(**Sensitivity and specificity of CTA using the latest 64 slice scanners has ranged from 91% to 100% and 81% to 100% respectively including distal pedal arteries. CTA can at times display eccentric stenoses and arterial segments distal to occlusions more accurately than angiography. Not only is the

technique accurate for gradation of stenosis but also for evaluating exact lesion length and number of stenoses which are important determinants in choosing the optimal therapeutic option. Vessel wall calcification decreases the clinical utility of CTA in patients with peripheral arterial disease.

MR Angiography (MRA)
MRA provides a minimally invasive approach for direct anatomic imaging of the peripheral vasculature. Two basic techniques are used for non contrast MRA – Time of flight (TOF) and Phase Contrast angiography (PCA). Three dimensional contrast MRA (CE-MRA) has substantially changed imaging strategies in patients with peripheral vascular disease. With CE-MRA signal of flowing blood is no longer flow dependent. Flow induced artifacts seen with non contrast MRA techniques are therefore largely eliminated. Metallic stents or clips however may produce artifacts significantly degrading image quality. The advantages of MR angiography include absence of ionising radiation, ability to depict larger vascular territories in 3D imaging volumes and absence of iodinated contrast media. Since risk factors like diabetes,cardiacdisease and age over 84 years are independently predictive for presence of vessel wall calcification, such patients may be considered for MRA as the initial diagnostic modality.3- Dimensional CE-MRA in recent years has become a well accepted imaging method for evaluation of Peipheral arterial vascular disease.

Use of dedicated peripheral vascular coils result in better signal to noise ratio and contrast to noise ratio as compared to body coils. The accurate grading of stensosis in the small calf and foot vessels requires high resolution imaging with an in plane resolution below $1mm^3$.

Nephrogenic systemic fibrosis has been reported in patients with impaired renal function, who have been administered the MR contrast gadolinium, the incidence being highest with gadodiamide.. It is preferable to use macrocyclic gadolinium chelates like gadoterodol or gadoterate meglumine which are more stable than linear chelates.

Conventional Angiography / DSA
DSA is the gold standard for arterial imaging. DSA uses image subtraction so that bones do not obscure vascular details. Contrast resolution is improved through use of image enhancement software, lower volumes of contrast medium can be used, and image acquisition is rapid. Angiography provides better anatomic detail and higher resolution than any other modality. Haemodynamic information regarding pressure gradients across stenoses can be obtained simultaneously. Most importantly percutaneous interventions like angioplasty, stenting, thrombolysis, thrombo-aspiration are possible at the same time.

DSA has certain limitations. It is an invasive procedure requiring intra-arterial catheters with resultant complications. The use of iodinated contrast media is associated with contrast reactions and nephrotoxicity especially in patients with renal compromise. Increasingly angiography is becoming a secondary imaging modality to resolve conflicting results of non invasive tests, or to confirm an abnormality prior to intervention. Surgical bypass can be performed on the basis of high quality US, MRA or CTA

Lower Limb Arteriography[9]

The procedure includes:

- Abdominal aortography***;*** bilateral lower extremity (run off) study; bilateral oblique pelvic arteriography; selective arteriography sometimes in multiple projections or after intravascular vasodilator injection to evaluate equivocal findings.

- Measurement of pressure gradients in the aorta and iliac arteries to determine the significance of moderate or suspicious stenoses.

Atherosclerosis
Typically diffuse, bilateral and often strikingly symmetric. Patients with claudication usually have single level disease, while patients with rest pain or more severe ischaemia have multilevel disease. Clinically relevant disease includes stenosis, thrombotic occlusion and ulcerated or exophytic plaques. Plaques may be characterised as focal or long, calcified or non-calcified, concentric or eccentric and smooth or ulcerated.

Arteritis

The most prevalent form of large vessel arteritis of the lower limbs Buerger's disease or thromboangitis obliterans. It typically affects young males and has a strong correlation with smoking. Lower extremities are involved in 90 per cent cases and upper extremities in 50 per cent cases.. CTA or MRA may not show any characteristic findings that distinguish it from atherosclerosis other than distribution of disease. The conventional angiographic findings are often striking. There is relative sparing of CFA, SFA and popliteal arteries with extensive involvement of medium and small arteries. Typically the disease is segmental and occlusions intervene with normal segments. Characteristic corkscrew collaterals are seen. Cessation of smoking is crucial and amputation is fairly common as reconstructive surgery or endovascular therapies are usually not possible due to lack of distal runoff vessels.

Upper Extremities- The brachiocephalic and left subclavian arteries are typically catheterised from the aortic arch. Significant atherosclerotic disease is less common in the arm. With proximal subclavian stenosis flow in the ipsilateral vertebral artery may be reversed resulting in subclavian steal syndrome. In uncomplicated Raynauds disease the arteries may be constricted but remain morphologically normal.

Aneurysms

An aneurysm is defined as focal or diffuse dilatation of an artery by more than 50 per cent of its normal diameter. Aneurysms are most often degenerative and they may be fusiform or saccular. Common sites for degenerative aneurysms in the extremities include iliac, popliteal and common femoral arteries in the lower limb and brachiocephalic and subclavian arteries in the upper limb. The entire popliteal artery may be aneurysmal, but focal aneurysms most often involve the vessel above the joint line.

Standard grey scale imaging can demonstrate the presence of either a focal bulge or more diffuse increase in arterial size. This diagnostic task is well performed by standard grey scale images that it now serves as a gold standard for the diagnosis of peripheral arterial aneurysms. It can visualize progressive deposition of mural thrombus not appreciated by arteriography. The sensitivity and specificity of ultrasound compared to surgery are close to 100 per cent. Doppler techniques are useful in confirming the continued patency of a channel within the thrombosing aneurysm either at presentation or following surgery.

CT Angiography demonstrates the exact size and extent of aneurysm, the presence of thrombus, presence of a patent lumen, and relationship of the aneurysm to adjacent bony structures.. Multiplanar reconstructions are particularly useful in planning surgical intervention providing information about the degree of extension of the aneurysm in sagittal and coronal planes and its relationship with adjacent structures. CE-MRA is an excellent technique for the diagnosis of aneurysms Aneurysms can be missed by catheter angiography if they are non-calcified and thrombosed or lined by mural thrombus. Catheter angiography is usually reserved for preoperative planning when percutaneous therapy is being considered or rarely when the diagnosis cannot be made by cross sectional imaging.

Pseudoaneurysms

In a pseudoaneurysm/false aneurysm one or more layers of the arterial wall are disrupted. Blood may be contained by the outer adventitia and surrounding connective tissue. The collection of blood remains in communication with the patent artery by means of a channel of variable size and length. The principal etiology is penetrating trauma and includes knife wound, bullet wound and medical intervention. Pseudoaneurysms of the CFA commonly develop following catheterization. Colour doppler is almost 100 per cent accurate in the diagnosis of pseudoaneurysms. The grey scale image shows an echolucent or mixed echogenic collection in close proximity to the artery. The colour flow image has a quite dramatic appearance: that of a swirl of colour sometimes referred to as the colour 'Yin – Yang' sign. This sign is not specific to pseudoaneurysms because saccular aneurysms share similar flow patterns. Colour flow mapping helps to locate the communicating channel which may be difficult to localise on grey scale imaging. The spectral waveform from the communicating channel shows a very typical pattern diagnostic of pseudoaneurysms and is called the 'to and fro sign' **.**During systole the pseudoaneurysm distends and stores energy. Blood flows quickly into the collection. During diastole the effective pressure within the collection is greater than the systemic arterial pressure thereby pushing blood out from the collection. Blood flow outwards is slower and has lower

amplitude.

CTA, MRA (esp. CE-MRA) and catheter angiography can also accurately diagnose pseudoaneurysms but are rarely required for diagnosis**.** Whenever, definitive pseudoaneurysm therapy is delayed frequent follow-up ultrasound examinations are recommended.

Surgical repair of post-catheterization femoral pseudoaneurysms is contemplated only when ultrasoundguided compression repair fails and the aneurysm continues to expand. In these cases Doppler may be used to mark the actual physical location of the communication obviating the need for preoperative angiography. Compression repair has also been successfully achieved in axillary and brachial arteries.

Arteriovenous Malformations

Arteriovenous malformations comprise an anomalous communication directly between an artery and a vein without an intervening capillary network. Clinically they present as pulsatile warm and sometimes painful masses). Colour Doppler shows a wide variety of flow patterns such as colour aliasing, colour persistence and colour bruit, spectral Doppler studies always show a high velocity low resistance and frequently turbulent flow.

CT and MRI are superior to ultrasound for demarcation of the boundaries of the lesion and for determining the relationship with adjacent structures. Three dimensional CE MRA can detect arteriovenous malformations or fistulas of the upper or lower extremities. It is helpful to obtain a multiphase exam in order to demonstrate early filling of the draining veins. It is useful to use a dedicated coil for evaluation of the AVM since high resolution images are desired. Angiography demonstrates markedly dilated inflow arteries, numerous feeding arterioles, pools of contrast within the AVM and early filling of draining veins.

Arteriovenous Fistulae (AVF)

It is always acquired from accidental or iatrogenic trauma. These can be quickly detected using Colour Doppler. They may present with local symptoms, distal ischaemia (from steal phenomenon) or a high output cardiac failure.

In large traumatic A-V fistulae, the diagnosis is easily made on Doppler by noting distention of a recipient vein with turbulent and in some cases pulsatile venous flow (arterialization of venous flow). The feeding artery has a monophasic turbulent continuous flow. The arterial Doppler signals distal to the lesion are likely to be normal. In some cases direct visualization of the communication is possible; however, this may not be always possible due to associated turbulence. An indirect sign of the fistula is dilatation of the vein and a poor Valsalva's response.

These findings may be absent in smaller A-V fistulae. In these cases colour flow imaging can locate the physical communication between the artery and the vein guiding placement of the Doppler gate exactly over the fistulous communication. Loss of high velocity signals in the recipient vein with Valsalva maneuver (i.e. positive Valsalva response) suggests that the communication is a small one and can be safely followed up without the need for an intervention. CTA or MRA can also be used to evaluate AVF. Good arteriography is important in demonstrating the anatomy of abnormal communication and requires a fast injection with adequate volume of contrast with early rapid serial filming to clearly define the anatomy and site of the fistula. The dilated feeding artery fills early and so does the dilated vein.

Acute Limb Ischemia

Prompt recognition of acute limb ischemia is vital to proper patient management. Only a narrow window of opportunity may exist in which to salvage the threatened limb. When acute limb ischemia is present, immediate diagnosis and intervention is necessary to restore blood flow.

A major diagnostic goal is the distinction between embolic and thrombotic occlusion. Embolic occlusions tend to result in profound ischemia owing to the absence of developed collaterals. Thrombosis of a pre existing stenosis is tolerated well because the collateral circulation is already established. The patient presents with a cold limb that is painful, pale or cyanotic and numb. Peripheral pulses are absent or diminished.

Imaging: Patients with critically ischemic limbs should proceed directly to surgery while those with less threatened limbs and extensive underlying vascular disease or complex vascular surgical history benefit from preoperative imaging Catheter angiography is the procedure of choice in most patients with acute limb ischemia, since patients require
Immediate intervention/surgery and when acute ischemia is suspected clinically patients usually proceed directly to catheter angiography

Angiography: An acute embolus produces a discrete filling defect with reconstitution of the distal vessels. However it may also appear as a sharp cutoff point that mimics a thrombotic occlusion. Angiographic signs of acute arterial embolism include a meniscus or filling defect, mild or absent disease in other vessels, lack of contralateral disease, poorly developed collaterals and emboli at other sites. In > 50 per cent cases emboli lodge in the brachial artery in the upper limb and the femoral or popliteal artery in the lower limb frequently at major bifurcations. Total occlusion can hide an unusual cause for thrombosis such as popliteal artery aneurysm. In patients with microembolization syndromes, proximal atherosclerotic disease or aneurysms are often found.

In thrombotic occlusions on the other hand evidence of diffuse atherosclerotic disease in the ipsilateral and contralateral limb is common. Usually collaterals are well developed and thrombosis produces midvessel occlusion rather than at vessel bifurcations.

CDFI, CTA and MRA can all depict arterial occlusion especially in the larger vessels, emboli in small vessels may be missed.

Trauma
The upper and lower extremity arteries are subject to injury from penetrating trauma, blunt trauma, fracture dislocations medical procedures chronic vibrational injury or use of crutches.

The increased acquisition speed of MDCT lends itself well to the emergency setting. Peripheral CTA can be performed within 10-15 min of room time. Due to good availability and fast scanning MD CTA may replace catheter angiography in the trauma setting. The main limitations for the use of MRA in trauma patients are logistic in nature. Patients in a critical condition, such as victims of multiple trauma are difficult to monitor properly in the MR scanner. These patients often have MR incompatible life supporting devices; hence the utility of MRA in trauma patients is limited.

Catheter arteriography is the most accurate technique for detecting traumatic injuries to the extremity arteries. Guidewires and catheters must be positioned away from the area of injury so that catheterization related vasospasm is not mistaken for vessel damage. The spectrum of angiographic abnormalities produced by trauma include intimal tears, intraluminal thrombus, vasospasm, intramural hematoma, dissection, transection with or without thrombosis, vessel deviation, A-V fistula formation, pseudoaneurysm formation and compartment syndrome which causes slow flow in proximal arteries.

Sonographic evaluation of traumatic arterial injury is controversial. At this time Colour doppler can be used safely to observe and to follow up lesions such as intimal flaps, pseudoaneurysm and AV fistulae. Doppler evaluation may be useful in patients with venous injury which may be undetected by angiography and a source of considerable morbidity.

Thoracic Outlet Syndrome (TOS)
The various forms of TOS are a distinct set of clinical disorders of the upper extremity caused by extrinsic compression of major nerves and blood vessels exiting or entering the thorax. In >95 per cent cases, symptoms are caused by compression of the brachial plexus and related nerves; arterial compression is responsible for only 1 per cent of cases. There are three locations in which thoracic outlet syndrome can occur –the scalene triangle, costoclavicular space and subpectoral space.

Imaging: Imaging is directed at evaluating both the lumen of subclavian artery and surrounding structures. The arterial lumen is imaged in order to confirm the compression and diagnose complications such as distal embolisation. Imaging should begin with a simple chest x ray which may reveal a cervical rib or other bony anomalies.

Colour Doppler may demonstrate extrinsic compression of the subclavian artery especially in abduction. Post stenotic dilatation may also be demonstrated. Cross sectional imaging of the upper

thorax with CT /CTA or MR/MRA is useful for evaluating both the artery and the surrounding structures. Bony abnormalities are well shown by CT while MR studies are particularly useful in characterizing fibro-muscular abnormalities. A complete angiographic examination from the arch to the hand is mandatory. Besides neutral position angiography may be performed in the position which provokes patient's symptoms, in which extrinsic compression of subclavian artery is demonstrated. However evocative maneuvers can induce arterial compression in half of normal patients. Other possible angiographic findings include aneurysm formation, distal embolization and complete thrombosis. The findings can be bilateral even when symptoms are not

Evaluation of Bypass Grafts

Colour flow imaging and duplex ultrasound are now the recommended noninvasive examinations for the post operative monitoring of bypass graft patency. They are used to detect focal stenoses before they progress and lead to graft occlusion.

The current approach to bypass graft imaging relies on colour flow image to identify sites of increased velocity seen as aliasing with appropriate PRF setting and spectral Doppler traces are then obtained from this site. PSV ratios are calculated compared to the normal segment, 2 to 4 cm proximal. Values above 2 are considered to represent lesions causing 50 per cent diameter narrowing or more. However in complex grafts, anastomotic sites may have high velocities with no stenosis. This is due to the anatomy of the anastomosis where a larger graft is attached to a smaller vessel or an area of vessel dilatation is constructed at the point where the graft joins the native vessel. In the distal anastomoses of aortobifemoral grafts for example stenosis should not be considered until the ratio exceeds 3 or 4.

MD-CTA and CE-MRA are at least as accurate as colour Doppler sonography for screening, but due to the longer procedure time and higher costs they are usually reserved for more complex cases. They, however, provide more thorough evaluation of the inflow and outflow vessels, often obviating the need for catheter angiography before surgery.

EVALUATION OF THE PERIPHERAL VEINS

Deep Venous Thrombosis

Acute DVT is a common problem with an overall lifetime risk of about 2 to 5%. A number of conditions are known to predispose to DVT. These include prolonged immobilization to hypercoagulability syndromes, trauma, and malignancy.

Sonography and Colour Doppler Flow

Sonography has revolutionized the diagnosis of deep venous thrombosis (DVT). The test is extremity accurate, easy to perform, relatively inexpensive and completely safe. It has essentially replaced contrast venography in diagnosing symptomatic patients. With optimal grey scale settings, the normal vein lumen is echo free with the exception of valve cusps Grey scale images also document intraluminal thrombus and compressibility. Normally with application of moderate pressure, patent veins collapse and anterior and posterior walls appose. The pressure required is generally less than that required to deform the adjacent artery.. Inability to completely obliterate the vein lumen with compression is the cardinal sonographic criterion for diagnosis of venous thrombosis**.** As the echogenicity of the thrombus is variable direct visualization of echoes within the venous lumen is less reliable. However direct compressibility is difficult to evaluate in the pelvis, adductor canal and calf veins.

Colour Doppler facilitates vessel identification and confirmation of patency of venous segments unable to be compressed directly. When using Doppler sonography DVT can be excluded when there is complete colour flow saturation of the entire deep venous system. Lack of colour fill in despite augmentation on the other hand suggests DVT.

There are several flow characteristics that are present in patent venous system which may be absent or altered with significant venous obstruction. These characteristics include spontaneous flow, cardiac and respiratory phasicity, the valsalva response and augmentation. Spontaneous flow should be present at rest but may not be present in veins of the calf and foot. The demonstration of a flow void or defect by colour Doppler, or absence of flow in a venous segment by colour or pulsed Doppler are findings highly suggestive of thrombus. Respiratory phasicity results from the normal flow velocity

changes that occur in response to variation in intrathoracic pressure. The presence of cardiac and respiratory phasicity in a vein suggests patency of the venous system between the thorax and site of insonation. When DVT is present, the venous segment distal to the thrombosis shows absence of respiratory phasicity. However respiratory phasicity may not be depressed in patients who are shallow breathers, who have spinal cord injuries and when the thrombosis is partial. Respiratory phasicity may be made more prominent by asking the patient to take a deep breath which results in cessation of flow. Evaluation of phasicity should be performed at both groins to facilitate comparison.

Augmentation entails mechanically propelling venous blood from distal portion of an extremity to the point of insonation by squeezing the calf. This results in a rush of blood which is detected by Doppler upstream, and is said to indicate absence of significant obstruction between the site of augmentation and insonation.

Isolated calf vein thrombi are difficult to detect by CDFI and anticoagulation controversial, so routine imaging of calf veins is not performed at many centers. Some studies demonstrate that a repeat above knee ultrasonography performed at day 5 to 7 after the first negative above knee study is all that is required to rule out significant DVT. While evaluating for lower limb DVT proximal portion of great saphenous should also be evaluated as thrombosis within this can extend into the deep system.

The sensitivity and specificity of sonography and Doppler in the diagnosis of DVT is 95 per cent and 98 per cent respectively in symptomatic patients. The sensitively and specificity are closer to 80% for calf DVT and asymptomatic patients due to higher incidence of isolated calf DVT and presence of smaller non occlusive segmental thrombi. Causes of misdiagnosis include - underlying chronic venous disease, isolated calf/iliac vein disease, venous duplication, small focal thrombi and technical errors.

Chronic DVT
About 48% of veins remain abnormal even after 6 months of the acute episode. There may be partial recannalisation,residual clot or organized thrombus.

The distinction between acute and chronic residua of venous thrombi is of great clinical importance as chronic thrombi are epithelialized and unlikely to embolise. However, sonographic distinction between acute and chronic DVT may be difficult to make and venography is the technique of choice. In chronic thrombosis the vein shows thickened walls, reduced caliber and may show patchy Since CDFI is a simple, accurate, non invasive diagnostic test for upper and lower extremity DVT, other cross sectional modalities are rarely indicated for diagnosing DVT.

CT Venography
Venography may be performed after helical computed tomographic pulmonary angiography for pulmonary embolism. In this setting evaluation can be made for both pulmonary embolism and lower extremity DVT without the need for additional contrast medium. Venous imaging may be performed afer a delay of 2 to 3 min. Arterial enhancement is however always present which can make identification of weakly opacified small veins difficult, Infusion of diluted contrast via a foot veins is feasible with multidetector technology but has found little clinical application in daily practise.

However CTV may prove to be useful in assessing the proximal extent of thrombus into the iliac veins or IVC in patients where these are difficult to evaluate by Doppler. Findings in acute DVT include filling defects encircled by a rim of contrast, venous dilatation and perivenous congestion. In chronic DVT, web like or thread like filling defects that are, peripherally located or calcified may be seen.

MR and MR Venography
This plays a limited role compared with ultrasound and contrast venography due to limited availability and high cost of examination. MR direct thrombus imaging (MR-DTI) is a technique which, allowing direct visualization of pulmonary emboli and simultaneous imaging of the legs without the need for intravenous contrast. flowing blood to maximize thrombus conspicuity.

CE-MRA may be performed by an indirect technique (i.e. following MR angiography) or by a direct technique using diluted gadolinium injection from pedal veins/antecubital vein.

Venography
The procedure is uncomfortable for the patient and has a small but definite risk of significant complications. For these reasons venography is infrequently performed.

The most reliable venographic findings is an intraluminal filling defect outlined by contrast. When the defect is smooth and fills a normal sized or enlarged vein, the thrombus is likely to be acute, i.e. less than 7 days. When the filling defect is contracted irregular and the vein is smaller than normal the thrombus is chronic.

Chronic Venous Disease

Imaging is central to the management of patients with chronic lower extremity venous disease. The most important determinants are patency of the deep system, valvular incompetence in superficial, deep and perforating veins, the extent of reflux and exact site of incompetent veins.

Sonography

Colour Doppler sonography is the standard tool for studying patients with venous insufficiency and varicose veins when invasive therapy is being considered. It can also identify venous reflux in the superficial and deep systems. If the deep venous system is normal, varicose veins is considered to be a primary problem. Sonography can also identify residual deep vein occlusion or partial recanalization. Reflux is defined as the retrograde flow of blood in veins of the lower extremity caused by absent or incompetent valves. Assessment of incompetence is performed by applying distal compression and observing the direction of flow. In the normal situation flow will not reverse following release of compression. If flow reversal for 0.5 sec to 2 sec is observed then incompetence is very likely while reversal of more than 2 sec is diagnostic. This must be performed with the patient standing and weight supported on the contralateral limb. Refluxing and non refluxing segments may be seen in the same vein. Assessment of reflux should be made in the superficial,especially saphenofemoral and saphenopopliteal junction and deep venous system separately. The more proximal veins may also be assessed following a Valsalva maneuver. In the normal condition there should be complete retardation of flow without flow reversal, should reversal be observed this is again evidence of venous incompetence. US with CDFI is >95% sensitive and specific for detection of reflux.

Perforating Veins

Incompetent perforating veins can also be identified by duplex sonography. One looks for veins coursing between the deep and superficial veins and then during manual compression and release one looks for bidirectional flow. Compression can be applied proximal or distal to the duplex interrogation site. In one study all perforators >4 mm were incompetent, irrespective of whether flow reversal was seen or not38 and those less than 3 mm were competent. Sonography can also be used to mark out the incompetent perforators however it may miss some incompetent perforators detected by venography, being about 80% sensitive but very specific. Doppler can also be used to evaluate patients postoperatively. In patients with varicose veins and reflux, superficial femoral venous reflux could be abolished by greater saphenous stripping. If the deep venous reflux persists after surgery the prognosis for cure of symptoms may be guarded. Ultrasound has also been used for guidance of radiofrequency or thermal ablation of saphenous vein for treatment of varicosities.

Venography

Ascending or descending venography is needed only when the results of duplex sonography are inconclusive, the study is technically inadequate or the anatomy is complex. The appearance of chronic DVT can vary from recanalised veins with narrow, irregular, web filled lumens with distorted valves and incompetent perforators to non- opacification of deep veins with preferential filling of superficial veins and collateral channels. Descending venography, though considered the gold standard is not without limitations. False positive results may occur due to seepage of high density radiographic contrast through a competent valve, also presence of a competent valve upstream does not allow evaluation of the valves located downstream.

In patients with primary varicose veins, descending venography, ascending venography or varicography may show filling of varicosities that communicate with valve less, dilated perforating veins.

CE-3D- MR Venography has also been performed in patients with recurrent varicosities after surgery and has the potential to affect clinical decisions in patients with recurrent varicose veins by helping to delineate complex venous anatomy.

Conclusion

Advances in non-invasive imaging modalities like Doppler sonography, CT angiography and MR angiography have greatly reduced the role of invasive arteriography/ venography. Although

therapeutic strategy may be planned on the non-invasive imaging techniques, angiography is often required for pre-interventional planning especially when the noninvasive modalities are inconclusive or technically inadequate.

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Work up of a patient with peripheral vascular disease

Pawanindra Lal

Work up of a patient with peripheral vascular disease largely depends on the diagnosis of whether it is a case of acute or chronic peripheral vascular occlusion. The standard set of investigations mentioned below is to determine the extent, site and nature of blockage in chronic peripheral arterial disease. The role of investigations in acute occlusion of the arterial system is limited to Doppler examination and conventional angiography for emergent non-invasive or invasive embolectomy or thrombectomy.

Investigations

1. Blood: Routine examination of blood including a hemoglobin percent (low Hb% can decrease claudication distances and aggravate rest pain), blood sugar examination as diabetics have worse prognosis, are essential. Erythrocyte sedimentation rate (ESR) is usually raised in Buerger's disease. In patients with high suspicion of underlying connective tissue disorders, specific test like

RA factor, LE cell phenomenon etc. may be carried out. Lipid profile is mandatory in elderly patients with atherosclerosis.
2. Urine examination for sugar.
3. Plain X-ray of the abdomen will show the presence of arterial calcification and flecks of calcium may outline an aneurysm.
4. ECG: an abnormality in ECG may influence the decision for surgery, in patients with lower limb disease.

Tests of Global Vascular Status

1. Hand Held Doppler ultrasound[1] blood flow detection uses a continuous wave ultrasound signal, beamed at an artery and the reflected beam is picked up by a receiver. The changes of frequency in the reflected beam, as compared with the transmitted beam, are due to the "Doppler shift", resulting from passage of beam through moving blood. These frequency changes are converted to audio signals. This investigation may be used effectively in cases where a differential diagnosis of atherosclerosis is entertained showing the site of block and extent of distal run-off. A 8-10 MHz continuous waver Doppler ultrasound probe is used to assess the posterior tibial (PT), dorsalis pedis (DP) and peroneal arteries. A normal pedal pulse produces a Doppler signal with 2 or 3 distinct phases with a clear sharp sounding systolic peak. The reduction in the pitch of this signal and a lack of the phasic components is recongnised as abnormal finding. In low arterial flow conditions, it becomes difficult to differentiate between arterial from venous flow. In such a situation, application of compression in the distal part of the limb would tend to augment in case of a venous signal but will leave the arterial signal unaffected. Recent study shows that it can be used effectively by students as well as clinicians.[2]

2. **Ankle Brachial systolic blood pressure index (ABPI)**[3] This measurement gives the quantitative assessment of the global limb arterial perfusion. Patient lies supine, all measurements are at the level of the heart and only after resting for 10-15 minutes. A standard BP cuff of 15-20 cm width is positioned in the ankle just above the malleoli. A 8-10 MHz Doppler ultrasound probe is used to hear the pedal Doppler signals and inflated above the systolic pressure for the signals to disappear. The point at which the Doppler signals first returns on gradually lowering the pressure marks the systolic pressure at the ankle level. Normally an average of 2 measurement for each of the arteries namely dorsalis pedis and posterior tibial is used to denote the ankle pressure. Similar procedure is done for brachial artery. The ratio of the highest recorded systolic pressure at the ankle to the brachial systolic pressure at the arm forms the ABPI. The ankle brachial index is interpreted in the manner as given in Table 4. As a thumb rule, patients with ABPI of 0.8 or 0.9 have moderate peripheral vascular disease, those between 0.5 to 0.8 suffer from intermittent claudication and those with < 0.5 may suffer from rest pain, ulceration or gangrene.

TABLE 1: – Ankle Brachial Pressure Index

ABI	Interpretation
1.1 ± 0.1	Normal
0.6 ± 0.2	Intermittent claudication
0.3 ± 0.1	Ischaemic rest pain
0.1 ± 0.1	Ischaemic ulceration or gangrene

"Segmental pressures", i.e. differences in arterial blood pressure between segments of limb can be detected to give indication of the sites of stenosis, specially as Buerger's is said to be a segmental disease.

3. **Toe Pressures Using Photoplethysmograph**: These are used when the arterial disease is suspected between the ankle and the toes. The measurement is done using a an occlusion cuff of 2-3 cm diameter placed around the great toe or 2nd or 3rd toe and the digital pulse is recorded by a photoelectric cell placed on the toe. The measurements are recorded on a strip chart recorder with cuff pressures being recorded simultaneously. Toe pressures are normally lower than the brachial or the tibial arteries at the ankle due to high resistance created by small digital arteries. Toe pressures are also indicated as a percentage of the brachial artery pressure referred to as the Toe Brachial Index (TBI). Normal ratio is 0.8-0.9. Patients with claudication have TBI of 0.2-0.5 and those with CLI have TBI<0.2

Fig 1: Toe Pressure measurement

4. **Pole Test**: This is used to determine the adequacy of lower limb blood flow in patients with incompressible vessels or who are unable to tolerate an ankle pressure cuff. It involves listening to the pedal pulse using the hand held Doppler probe while the patients leg is raised against a pole. The height at which the Doppler signal disappears is reflected by the markings in mm Hg in a calibrated pole directly. A maximum of 60-70 mm Hg only can be recorded since the test is limited by the height upto which the patient is able to lift the leg.

Fig 2 Pole test using Doppler probe

5. **Transcutaneous Oximtery (TcPO2)**[4]: It is based on the principle that the partial pressure of the oxygen which diffuses through to the surface of the skin reflects the oxygen tension of the underlying tissues. It is time consuming and is best used in the selection of amputation sites since it correlates well to subsequent stump healing.

6. **Walk Test**: The basis of this test is that measurement of ABPI before and after a patient has walked can expose less severe or compensated peripheral vascular disease. The walk can be standard or graded (incline) using a tread mill. A reduction in ABPI of >20% indicates presence of severe arterial disease. In normal limbs, there is a rise or status quo in the ABPI. As a rough guide, post exercise ABPI of 0.8-0.9 confirms claudication caused by moderate disease, 0.5-0.7 indicates significant disease and <0.5 denote severe arterial insufficiency.

Fig 3 Walk Test on the Tread Mill

Tests for Disease Localisation

1. **Duplex imaging**[5] gives accurate information on the size of artery, the flow rate, turbulence and the presence of stenosis. The combination of Doppler and color mapping allows easy recognition of stenotic sites. This has been achieved by the use of pulsed or continuous wave Doppler and the two- dimensional images produced by the B- scan made either singly or in combination. Peak systolic velocity at the site of stenosis is compared to that measured proximally to obtain a peak systolic velocity ratio (PVR) and relates to the degree of stenosis. A 2x increase in PVR at a stenosis corresponds to 50% reduction in diameter on arteriography. This modality is non invasive and has now become the mainstay of assessment of arterial insufficiency, and has largely replaced routine use of conventional arteriography. This requires detailed assessment of each major arterial segment i.e Aorta, Iliacs, Femoropopliteal and infrapopliteal segments. This investigation has virtually become the first line investigation to localize the level of block with a great deal of accuracy.

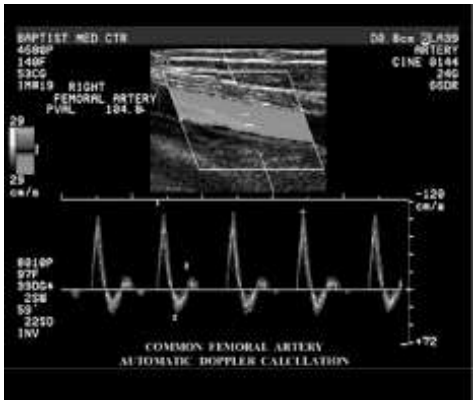

Fig 4: Duplex Imaging

2. **Intravascular Ultrasound**[6]: Minute ultrasound probes with 10MHz transducers mounted on tips of small 3-4 F catheters are placed directly in the lumen of the arteries over a guidewire and produce intravascular ultrasound images which give details of arterial walls, luminal contents and dimensions. This is not a routine investigation for peripheral arterial disease and as yet is not cost effective.

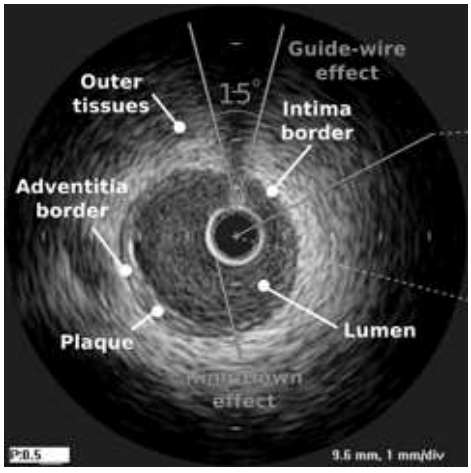

Fig 5: Intravascular Ultrasound

3. **Arteriography**[7]: This is an invasive technique which though has become much safer in the recent years due to fine 3-4 F catheters, and remains the gold standard to provide a road map required for vascualt surgeons expecially before surgery is planned. However, alternative modalities have emerged which seem more attractive and safer largely because they are non invasive and lack the potential hazards of arteriography like allergies to contrast agents, use of ionizing radiation, and technique related problems like hematoma, arterial spasm, sub-intimal

dissection, infection, pseudoaneurysm, AV fistula and embolisation. Angiography remains still the preferred investigation before percutaneous transluminal angioplasty or definitive bypass surgery is performed but is slowly being pushed away by the following non invasive techniques as they are improving with technology.

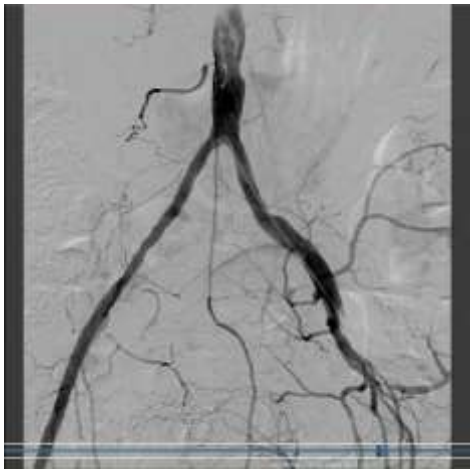

Fig 6: Invasive Angiography

4. **CT Angiography**[8]: The introduction of the helical (spiral) CT scanning and multidetector CT which uses 2 or 4 helicals to scan the patient, CT imaging has been revolutionized for vascular imaging wherein a single breathhold time is sufficient to generate the scans from the aortic arch to the groins with imaging quality as good as conventional angiography. However, it still uses ionizing radiation and iodinated contrast agents and therefore it has not yet gained usage for peripheral arterial disease. It is however, the imaging of choice for pre-operative assessments of aneurysms.

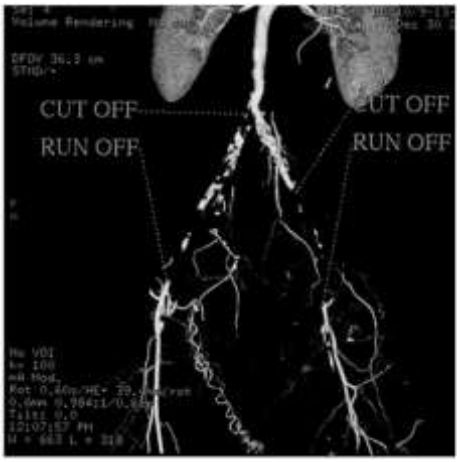

Fig 7: CT Angiography showing Cut off and Distal Run Offs

5. **MR Angiography**[9]: Increasing usage of Magentic Resonance Imaging in the last decade and improvement in technology has seen a shift towards using this modality for assessment of vascular system especially as a screening investigation for peripheral vascular disease. Earlier, Time of Flight MRI and Phase Contrast MRI were used to visualize moving blood as a white image but the definition and clarity of the vessels was found to be inferior to angiograms. More recently, Gadolinium Enhanced MRI (Gd-MRI) has significantly improved this quality of image and made it comparable to conventional angiography. The disadvantage is the high cost of the contrast material and availability of the MRI technology. As of now Gd-MRI is being used more often for assessment of peripheral limb ischaemia in combination with Dupleix Scanning and Conventional catheter angiography has been reserved where findings of these two investigations are discordant.

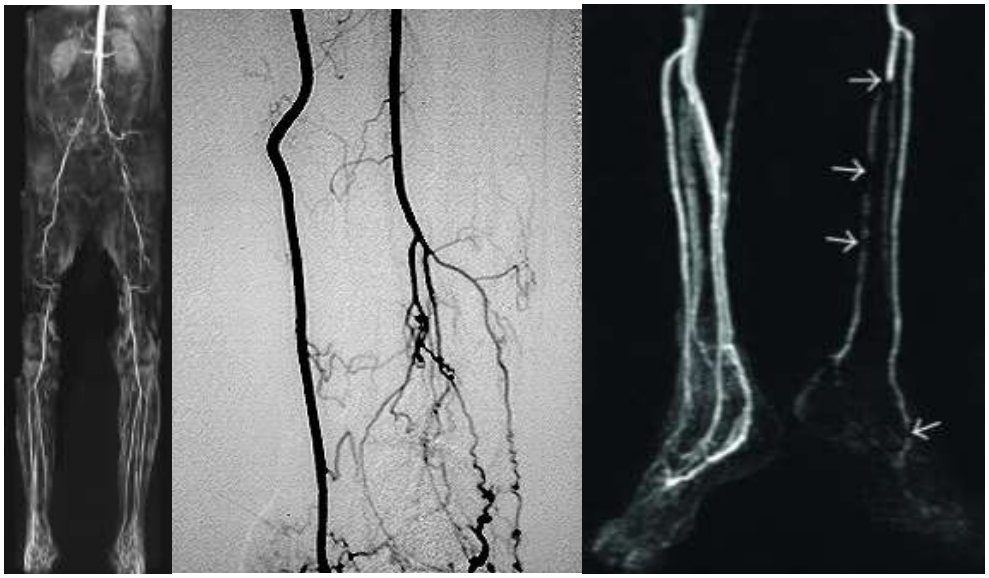

Fig 8: MR Angiography showing Block at the Aortic Bifurcation
Fig 9: MR Angiography showing the block in the posterior tibial artery
Fig 10: MR Angiography showing cork screw"vessels in Buerger's Disease

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Lower Limb Amputations

Anurag Mishra

History and Introduction

The word amputation is derived from the Latin *amputare*, "to cut away", from *ambi-* ("about", "around") and *putare* ("to prune"). In past most writers used the words "extirpation" (16th-century French texts tended to use *extirper*), "disarticulation", and "dismemberment" or simply "cutting", but by the end of the 17th century "amputation" had come to dominate as the accepted medical term.

Amputation is the most ancient of all surgical procedures. Amputation of a hand or foot was a common punishment in many of the older so-called civilized societies and is still carried out today in some countries. In those times, surgical amputation was a crude procedure by which a limb was rapidly severed from an unanesthetized patient; for hemostasis the open stump was crushed or was dipped in boiling oil. This procedure was associated with a high mortality rate. For those who survived, the resulting stump was poorly suited for prosthetic fitting.

Early in the sixteenth century amputation surgery and prosthetics were much improved by Ambroise Paré, a French military surgeon. Paré created more functional stumps and was the first to use ligatures to control bleeding after amputation; he also designed relatively sophisticated prostheses. Refinements of surgical technique such as hemostasis, anesthesia, and improved perioperative conditions have occurred. Modern total-contact prostheses can be fitted satisfactorily on any properly constructed and well-healed lower extremity amputation stump, usually resulting in excellent function.

However amputation is still often viewed as a failure of treatment. The responsibility for performing an amputation may even fall on the most junior member of the surgical team. Whatever the reason for performing an extremity amputation, it should not be viewed as a failure of treatment.

Indications of Amputations

Overall, indications of surgical amputations have been classified as

1. Dead (or Dying)
    i. Peripheral vascular disease – 90%
    ii. Severe trauma,
    iii. Burns, frostbite.
2. Dangerous/ Deadly
    i. Malignant tumors,
    ii. Lethal sepsis,
    iii. Crush injury.
3. Dead loss
    i. Intractably painful (post radiotherapy, post op brachial neuralgia)
    ii. Gross malformation, congenital anomalies,
    iii. Recurrent sepsis, chronic osteomyelitis,
    iv. Severe loss of function, flail limb (polio),
    v. Combination of deformity and loss of sensation.

According to disease, indications can also be classified as:

A. Peripheral vascular disease
B. Trauma
C. Infection
D. Tumors
E. Congenital anomalies/deformities
F. Thermal burns/ Cold injuries
G. Miscellaneous

A. **Peripheral vascular disease:** Most frequently occurs in individuals between 50 – 70 years. It is by far the most common indication for amputation. Before performing an amputation for peripheral vascular disease, all medical problems require treatment individually. Infection should be controlled as effectively as possible, and nutrition and immune status should be evaluated with simple screening tests.

B. **Trauma:** Trauma is the leading indication for amputations in younger patients. Factors which predicts indications for amputation are:
    1. Energy that causes the injury.
    2. Limb ischemia
    3. Shock
    4. Age

C. **Infection:**
    1. Bone infection (osteomyelitis)
    2. Diabetes
    3. Frostbite

    Open amputation is indicated in this setting and may be performed using one of the two methods.
        i. A Guillotine amputation may be performed with later revision to more proximal level after infection is under control.
        ii. Alternatively an open amputation may be performed at the definitive level by initially inverting the flaps and packing the wound open with secondary closure at 10-14 days.

D. **Tumors:** Indications include: -

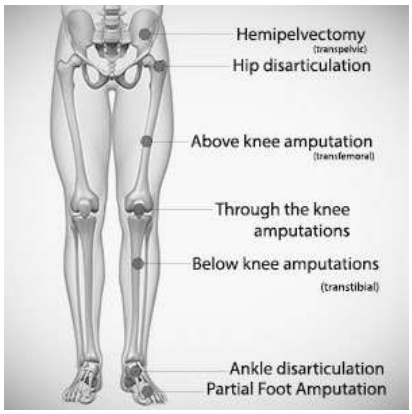
1. Primary malignancy e.g. Bony tumors, melanomas, soft tissue sarcomas, advanced skin tumors
2. Palliative measure in patients with metastatic disease.
3. Pain refractory to standard surgical treatment, radiation, chemotherapy & narcotic pain management.
4. Recurrent pathological fracture.
5. Malignancy causing massive necrosis, fungation, infection, vascular compromise.

E. **Deformities**

1. Deformities of digits and/or limbs (e.g. proximal femoral focal deficiency)
2. Extra digits and/or limbs (e.g. polydactyly)

Levels of Lower limb amputation

- Amputation of digits
- Partial foot amputation (Chopart, Lisfranc, Ray)
- Ankle disarticulation (Syme, Pyrogoff)
- Below-knee amputation
- Knee disarticulation (Gritti or Gritti-Stokes)
- Above-knee amputation (transfemoral)
- Vanness rotation/rotationplasty (foot being turned around and reattached to allow the ankle joint to be used as a knee)
- Hip disarticulation
- Hemipelvectomy/hindquarter amputation



Amputation of Digits

Amputation of a single toe usually causes little disturbance in stance or gait. Amputation of the great toe does not materially affect standing or walking at a normal pace. If the patient walks rapidly or runs, however, a limp appears because of the loss of push-off normally provided by the great toe. Amputation of the second toe frequently is followed by severe hallux valgus. Amputation of any of the other toes causes little disturbance.

Technique of phalangeal amputation

Fashion a long plantar and a short dorsal skin flap. Begin the incision at the level of intended bone section at the midpoint on the medial side of the toe and curve it over the dorsal aspect to end at a similar point on the lateral side. Now fashion a similar plantar flap but make it slightly longer than the dorsoplantar diameter of the toe at the level of bone section. Dissect the skin flaps proximally to the level of bone section. Divide the flexor and extensor tendons and let them retract just proximal to the end of the bone. Isolate and divide the digital nerves and ligate and divide the digital vessels. Then section the bone at the selected level and smooth its end with a rasp. Close the flaps with interrupted nonabsorbable sutures.

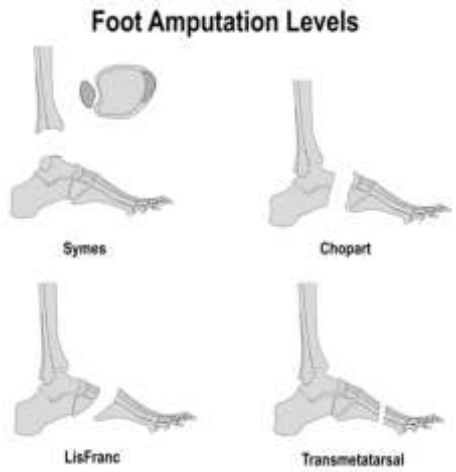
Technique of amputation at base of proximal phalanx

The skin incision varies with the toe involved. For instance, make a long posteromedial flap if the procedure involves the great toe. Begin the incision at the base of the toe in the midline anteriorly and curve it distally over the medial and posteromedial aspects for a distance slightly greater than the anteroposterior diameter of the digit; then extend it proximally across the plantar surface of the toe to the web. During closure reflect this flap laterally and suture it to the medial edge of the skin in the web. In the second, third, and fourth toes amputation is performed through a short dorsal racquet-shaped incision. Begin the incision 1 cm proximal to the metatarsophalangeal joint and pass it distally to the base of the proximal phalanx, dividing it to pass around the toe and across the plantar surface at the level of the flexor crease. After amputation close the wound by side-to-side approximation of the skin edges. In the fifth toe fashion a lateral flap long enough to cover the defect left by the

amputation. Then close the wound by approximating the flap to the skin in the web. In each instance, after making the incision, reflect the flaps proximally to the level of bone section. Draw the tendons distally, divide them, and allow them to retract. Then identify the digital nerves and divide them proximal to the end of the bone and divide and ligate the digital vessels. Close the skin edges with interrupted nonabsorbable sutures.

Foot Amputation

Amputation through the metatarsals is disabling in proportion to the level of amputation: the more proximal the level, the greater the disability. The loss of push-off in the absence of a positive fulcrum in the ball of the foot is chiefly responsible for impairment of gait. Again, no prosthesis is required other than a shoe filler.Amputations more proximal than the transmetatarsal level result in considerable awkwardness in walking caused by loss of support and push-off. Consequently most amputations of the forefoot and midfoot have been discarded. Occasionally, however, such procedures are indicated, especially in diabetic patients and less often after severe trauma.



Lisfranc amputation at the tarsometatarsal joints often results in an equinus deformity because of loss of the foot dorsiflexor attachments.

Chopart amputation through the midtarsal joints may result in a severe equinovarus deformity.

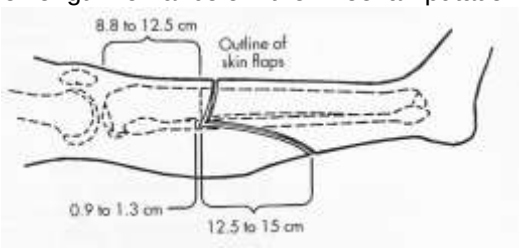
Syme amputation: through distal tibia and fibula 0.6 cm proximal to the periphery of the ankle joint and passing through the dome of the ankle centrally. The tough, durable skin of the heel flap provides normal weight-bearing skin.

Leg Amputations (Below Knee)

Although many variations in technique exist, basically all procedures may be divided into those for nonischemic limbs and those for ischemic limbs. These two general techniques vary primarily in the construction of skin flaps and in muscle stabilization techniques.

Nonischemic Limbs

The ideal level for amputation below the knee is at the musculotendinous junction of the gastrocnemius muscle. That part of the leg distal to this level, that is, the distal third of the leg, is not satisfactory because there the tissues are relatively avascular and soft tissue padding is scanty. In this part even stumps that heal well at first may break down later because of prosthetic use and physiological changes of aging. In adults the ideal bone length for a below-the-knee amputation stump is 12.5 to 17.5 cm, depending on body height. A reasonably satisfactory rule of thumb for selecting the level of bone section is to allow 2.5 cm of bone length for each 30 cm of body height. A stump under 12.5 cm long is less efficient. Stumps less than 5 cm long are not functional at all.



Ischemic Limbs

Because the skin's blood supply is much better on the posterior aspect of the leg than on the anterior or anterolateral side, below-the-knee amputation techniques for the ischemic limb are characterized by skin flaps that favor the posterior side of the leg. The long posterior flap technique popularized by Burgess is most commonly used. All techniques stress the need for preserving intact the vascular connections between skin and muscle by avoiding dissection along tissue planes and by constructing myocutaneous flaps. Also, amputations performed in ischemic limbs are customarily at a higher level, for example, 10 to 12.5 cm distal to the joint line, than are amputations in nonischemic limbs. Tension myodesis and the osteomyoplasty procedure of, which may be of value in young, vigorous patients,

are contraindicated in those with ischemic limbs because the procedures tend to compromise an already precarious blood supply.

Thigh Amputations (Above Knee)

Amputation through the thigh is second in frequency only to below-the-knee amputation. Because in this procedure the patient's knee joint is lost, it is extremely important that within the limits mentioned here the stump be as long as possible to provide a strong lever arm for control of the prosthesis. The conventional, constant friction knee joint used in most above-the-knee prostheses extends for 9 to 10 cm distal to the end of the prosthetic socket, and the bone must be amputated this far proximal to the knee to allow room for the joint. When the level of amputation is more distal than this, the knee joint of the prosthesis will be more distal than the knee of the opposite limb; this is cosmetically undesirable and is especially noticeable when the patient is seated.

In nonischemic limbs, muscle stabilization by myodesis or myoplasty is important when constructing a strong and sturdy amputation stump. Most amputations, even at the above-the-knee level, are done because of ischemic problems, and myodesis should not be attempted lest a limited vascular supply be further compromised.

Amputations of Hip and Pelvis

Hip and pelvic amputations include those performed through the femur from 5 cm distal to the lesser trochanter proximally, disarticulations of the hip, and hindquarter amputations. Although immediate prosthetic fitting can be accomplished at these levels, the available apparatus is poor. The surgical sites mature so rapidly that definitive prostheses can be fitted early. Therefore conventional soft dressing techniques are recommended as standard aftertreatment. The definitive prosthesis for all these levels is a Canadian hip disarticulation prosthesis or a modification of it.

Hindquarter Amputation

Hindquarter amputation is also known by the following synonyms: interinnominoabdominal amputation, interilioabdominal amputation, interpelviabdominal amputation, ilioabdominal amputation, transiliac amputation, transpelvic amputation, and hemipelvectomy (Jaboulay amputation).

The operative technique follows the same general pattern found in the various methods described. The patient is placed with the sound side downward in the full lateral position or tilted slightly posteriorly. The anterior incision starts at the pubic tubercle and swings superiorly and laterally either at or slightly proximal or distal to the inguinal ligament and then along the crest of the ilium as far as necessary to resect the desired amount of the pelvic ring posteriorly. The posterior incision starts at this point and swings distally and anteriorly around the greater trochanter, then posteriorly and medially at or inferior to the gluteal fold, and then superiorly into the crease between the adductor muscles and the perineum. The perineum and the abdominal contents and spermatic cord are reflected medially. If section of the posterior ilium is carried out far enough anteriorly to retain the gluteus maximus in the posterior flap, ligation of the external iliac artery alone should be carried out. The internal iliac artery which supplies the subcutaneous fat of the posterior flap should be preserved. The symphysis pubis should be divided before the bone is divided posteriorly. The latter division may be carried out with a saw or chisel, Muscles and other vessels are sectioned, and flaps are closed with interrupted sutures.

Open Amputations

As the name implies, an open amputation is one in which the skin is not closed over the end of the stump. Open amputations are indicated in infections and in severe traumatic wounds with extensive destruction of tissue and gross contamination by foreign material. The operation is only the first of at least two operations required to construct a satisfactory stump. It must always be followed by secondary closure, reamputation, revision, or plastic repair.

The purpose of this type of amputation is to prevent or eliminate infection so that final closure of the stump may be carried out without breakdown of the wound. Appropriate antibiotics are given until the stump is finally healed.

Open amputations are of two general types:

- open amputations with skin flaps and
- circular open amputations.

Open amputation with inverted skin flaps should be preferred over circular method because the wound is allowed to drain freely and is usually ready to close secondarily within 10 to 14 days without shortening the stump. In contrast, circular amputations are often treated by reamputation at a more proximal level.

General principles of amputations

1. *Clean operative field*: Pre-operative aseptic skin care should be taken. Fresh wounds should be cleaned & debrided. Old wounds should display healthy granulation tissue.
2. *Tourniquet*: Except in ischemic limbs the use of a tourniquet is highly desirable and makes the amputation easier Usually the limb should be exsanguinated by wrapping it with a bandage before the tourniquet is inflated. However, in amputations for infections or malignant growths, expressing blood from the limbs in this manner is inadvisable; in such instances inflation of the tourniquet should be preceded by elevation of the limb for 5 minutes.
3. *Level of amputation*: As much of the length as is consistent with good function should be preserved. Trade off lies between increased function with more distal level of amputation and decreased complication rates with a more proximal level of amputation. Too short stump leads to slipping out of prosthesis, whereas too long stump is associated with inadequate circulation become painful, ulcerate. It is also associated with complicated incorporation of joint in prosthesis.

   Surgery should be performed through as normal tissue as possible to enhance wound healing and at a level most suited for prosthesis. With modern prosthesis, any level of amputation acceptable.

   Ideal Level: Certain sites are preferred, determined by types of prosthesis, function of part, muscle balance and adedquacy of circulation.

   - Transtibial: Ideal level is at musculotendinous junction of gastronemius.
     - Ideal length is 12.5-17.5cm or 1 inch of bone length for each feet of body height
     - For ischemic limb- 12 cms
     - Minimal useful length- 9 cm or flex the knee to right angle; the residual tibia should extends at least 3 fingerbreadths beyond the insertion of med. Hamstrings.
     - Fibula is divided 1cm prox. to the tibia

   - Transfemoral: Shortest length for effective use of prosthesis – 8 cm. Ideal length is 13 cms.

   In cases of vascular insufficiencies, level is determined by:

   - Clinical findings:
     - Tissue appearance,
     - Skin temp,
     - Presence/ absence of edema after elevation,
     - Hair growth,
     - Presence of pulses,
     - Sensation level
   - Lab findings
     - Doppler study
     - Themography
     - Laser doppler flowmetry
     - Transcutaneus O2 measurements
   - Surgical findings
     - Adequate bleeding
     - Tissue viability

4. Skin flaps: Ends should be covered with good mobile skin of adequate thickness and normal sensation. With introduction of modern total contact prosthesis location of scar is unimportant. Avoid adherence to underlying bone & redundant skin. Their combined length should equal one and a half time the width of the limb at the site of amputation.

Flap length: depending on site of amputation

- Hip: Racquet incision – scar away from fecal contamination & pressure area over ischial tuberosity.
- Above knee: long ant/ short post
- Below knee:
    - Circulation adequate –equal ant/post flaps to allow scar to lie transversely immediately behind tibia
    - Ischemic limb – more vascular posterior flap longer, scar anterior above the bone end.
- Symes: long post (more vascular)/ short ant.

5. Muscles: In conventional amputation the level of muscle section is just distal to the level of bone section. When muscle retracts, it reaches level of bone section. Skin must not be separated from the tendons or muscles when configuration of both is identical – aids in grouping of muscles about the side of bone. Bulky muscle mass is avoided over bone ends. Muscle is beveled and contoured to obtain a properly shaped cylindrical conical stump.
   Stabilization of muscles over bone
   - Myodesis : Fixation of muscles to bone. Myodesed muscles continue to counter balance their antagonist, preventing contracture. Myodesis is contraindicated in severe ischemia because of increased risk of wound breakdown
   - Myoplasty : Bringing of muscle over bone ends & fixing it to opposite muscles.
6. Nerves: Nerves are isolated, pulled down gently, sectioned and allowed to retract beyond saw line. Strong tugging and irregular section predisposes to neuroma formation, phantom limb sensation and should be avoided. Larger nerves should be ligated before sectioning.
   Other methods
   - Injecting nerves with a local anesthetic agent
   - Bury the nerve ends in bone or muscle
   - Cap them with Silastic
7. Blood vessels: Major blood vessels – isolated, doubly ligated with non- absorbable sutures & then cut. Tourniquet is released before closure & hemostasis achieved.
8. Drain: Kept for 48 -72 hours to Prevent post op hematoma & infection.
9. Bone: Periosteum cut at the saw line. Bone cut transversely except in end bearing stumps where it is cut parallel to ground. Bone edges are rounded off with a file.
10. **Post operative management:** The rigid dressing method of postoperative stump management employs a plaster of Paris cast applied to the stump in the operating room at the conclusion of surgery. A number of benefits may be derived from the use of rigid dressings. The technique prevents edema at the surgical site, and this enhances wound healing and early maturation of the stump. Rigid dressings decrease postoperative pain and probably allow earlier resumption of the erect posture and ambulation with support.

Complications of Amputations

- **Infection** – more common in amputations for peripheral vascular disease, especially in diabetic patients.
- **Necrosis** – minor necrosis of skin edges can be treated conservatively. More severe necrosis, however indicate insufficient circulation at the level of amputation and immediate wedge resection or re-amputation at a more proximal level is necessary. preoperative determination of local tissue perfusion and oxygenation by such techniques as Doppler ultrasound measurement of segmental blood pressures, radioactive xenon clearance tests, and transcutaneous oxygen measurements prevents this complication.
- **Contractures** - Contractures of the joints of an amputation stump should be prevented by properly positioning the stump and by having the patient engage in exercises to strengthen the muscles and mobilize the joints. Any mild or moderate contracture that does occur is treated by appropriate positioning of the stump, gentle passive stretching of the joint, and by having the patient exercise to strengthen the muscles controlling the joint. Severe fixed contractures may require treatment by wedging casts or by surgical release of the contracted structures.

- **Phantom sensations:** Following amputation, an individual feels as if the non-existent limb were still present. It may feel exactly like the original limb as to shape, size, position and ability to move. The sensory phenomenon has been characterized as being of three types, a mild tingling sensation, a stronger momentary “pins and needles” sensation and an intermittent disagreeable twisting, pulling or burning sensation. Upper limb phantoms are stronger and longer lasting than those of the lower limb. The phantom persists for varied periods of time and has been reported to continue from 6 months to 20 years. As phantom disappears, it usually undergoes a change in perception known as telescoping, in which hand or foot feels as if it were directly attached to the proximal stump. The last parts of the phantom to disappear are those that are best represented in the cortex, such as the thumb and index finger.

- **Phantom pain:** The mechanism of phantom pain remains controversial. A central mechanism has been proposed in which the reticular formation exerts an inhibitory influence on transmission at al synaptic levels of the somatic projection system. The amputation process destroys a significant number of sensory axons to the reticular formation and the inhibitory influence is diminished. This results in self-sustaining neural activity at all levels that can be initiated by the remaining axons. If the self sustaining activity reaches a critical level, the result is pain. The patient with phantom pain resulting from physical disease usually can be distinguished from the psychogenic pain – the patient with physical disease usually has a period of no pain following amputation and the pain follows the nerve distribution. The patient with psychogenic problems usually has pain immediately following amputation, the pain does not follow nerve distribution and it is evoked especially by reference to disturbing events.

  There are four major characteristics of the phantom limb pain
  a) The pain endures long after healing of the injured tissues and may last for years
  b) Trigger zones may spread to healthy areas and stimulation of these zones will produce pain.
  c) Phantom limb pain is more likely to occur in patient who have suffered pain in the limb for a long duration
  d) Phantom pain may be abolished by changes in somatic input

  Phantom pain may be relieved by hypnosis or distraction conditioning. Use of narcotics may be dangerous in this problem and these drugs should be withheld as it leads of high incidence of drug addiction. The two principles of in the treatment of an established pain syndrome involving the amputee’s extremity are
  a) Relieve the pain
  b) Institute active use of the involved extremity

- **Reflex sympathetic dystrophy:** Also known as causalgia, Leriche’s posttraumatic pain syndrome, sudek’s arophy or shoulder-arm-hand syndrome. The loss of vascular, sudomotor, pilomotor and muscle tone controls result in profound nutritional (trophic) changes. There is atrophy of subcutaneous tissue, skin, muscle and bone. In the early stages the residual limb is markedly swollen and warm. There is hypersthesia to light touch and sensitivity to cold. After two or three months, there is fibrotic brawny edema. Contractures become fixed due to lack of active motion. There is patchy osteopenia. Six to nine months after the onset of pain, the extremity becomes pale and cool with either hyperhidrosis or dryness. Pain may dominate or the extremity may be absolutely rejected by the patient.

  The syndrome is thought to be a prolongation of the normal sympathetic response to injury. The pain impulses to the cortex greatly amplified, causing intense discomfort. The partial injury to a major nerve results in abnormal cross-stimulation between sympathetic ad sensory fibers resulting in reflex sympathetic dystrophy.

  Early treatment is interruption of the abnormal sympathetic reflex and a chemical central sympathetic block should be performed. Surgery should be performed when the burning pain responds to central chemical sympathectomy. Surgical sympathectomy will relieve burning pain but not pain associated with neuroma or arthritic pain.

- **Neuroma:** The development of neuroma is normal after trisection of a peripheral nerve. A large neuroma buried in scar or located in an exposed position may become painful. During the

amputation procedure the nerve should be identified and a single ligature should be placed just proximal to the point of transaction. Gentle traction of the nerve before transection will allow the nerve to retract into an adequate bed of soft tissue. A painful stump is the most common reason for revision and often reflects a lack of careful attention to the technique and level of nerve division.

Percutaneous injection of triamcinolone acetonide about the neuroma after cutaneous block with lidocaine hydrochloride relieves pain syndrome in majority of patients. The steroid softens the fibrous tissue about the neuroma. The best surgical procedure for a painful neuroma is transfer of the neuroma, attached to the proximal nerve stump, to a new site where compression is unlikely and traction is minimal. The neuroma should be placed in an area of good circulation with a thick subcutaneous layer that is free of scar.

- **Prosthetic pain:** When the patient complains of discomfort after prosthetic fitting, efforts should be made to eliminate irritation of the soft tissues. Ther may be localized stump pain, reactive hyperemia of the skin, an underlying bursa or occasionally skin ulcer. Fixed scar is unyielding to shear forces and produce pain.

  Appropriate padding og the prosthetic socket to regain satisfactory contact often relieves pain. Stump revision is indicated when there is bony overgrowth, a chronic bursa, poor skin coverage, or extreme soft tissue redundancy.

- **Emotional response of the amputee:** With traumatic amputation, patients pass through three rather well defined phases of response.
  a) First is phase of disbelief and denial. Generally this shock like situation is very brief and occurs in hospital where ready assistance is available and reassurance is given. Most patients tolerate this phase remarkably well.
  b) Second phase is of anxiety for the situation and all its implications for the future. A time for frustration, disillusionment and often hostility, when the patient leaves the sheltered atmosphere of the hospital and the real impact of what has happened hits the patient.
  c) Third phase is the acceptance of the loss, attributing appropriate importance to it and achieving progressive adjustment with the use of all remaining assets.

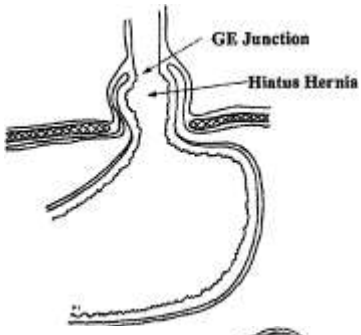
Hiatus (Paraesophageal) Hernia: Clinical Presentation, Evaluation, and Management Controversies

Sabyasachi Bal

Few topics within thoracic surgery are as controversial as the management of paraesophageal hernias (PEH). In this article, the types of hiatal hernia are classified and the clinical presentation and evaluation of patients with PEH are discussed. Controversies in the management of PEH including the indications for surgery, the different operative approaches, and the role of esophageal shortening are reviewed. Finally, the evidence regarding the need for fundoplication or fixation of the stomach with gastropexy or gastrostomy and the use of prosthetic material in performing the hiatal closure are examined.

There are many types of diaphragmatic hernias and the terminology used to classify them is often confusing. The common feature of all is that some portion of the stomach has been displaced into the thorax. Anatomically, there are hernias through the diaphragmatic esophageal hiatus and those distinct from the hiatus. The latter are more correctly called “parahiatal diaphragmatic” hernias, the classic examples being congenital hernias through the diaphragmatic muscle proper, such as a Bochdalek or Morgagni hernia. This article addresses hernias through the esophageal hiatus.

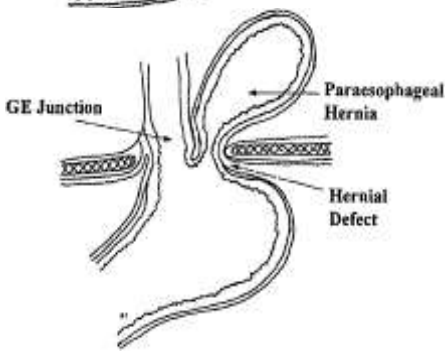
When describing hiatal hernias, the traditional classification is favoured, which defines the hiatal hernia according to the position of the gastroesophageal junction (GEJ) and the extent of herniated stomach.[1]



Type I hiatal hernia is a sliding hernia that occurs with migration of the GEJ into the posterior mediastinum through the hiatusbecause of laxity of the phrenoesophageal ligament (Fig. 1). This type accounts for more than 95% of hiatal hernias.[2], [3]

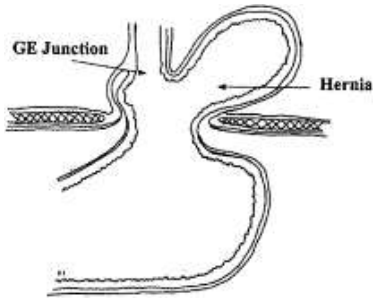
Most small type I sliding hernias are asymptomatic. When they enlarge, the predominant symptom is gastroesophageal reflux.[4] This is a complex and separate clinical problem and beyond the scope of this article and will not be discussed any further.

Type II is a true paraesophageal hernia (PEH), which occurs when the fundus herniates through the hiatus alongside a normally positioned GEJ by a defect in the phrenoesophageal membrane (Fig. 2). This is the least common type of hiatal hernia.[5]



Type III is a combination of types I and II hernias with cranially displaced GEJ and stomach through the hiatus (Fig. 3). As the hiatal hernia enlarges and more stomach herniates, volvulus of the intrathoracic stomach may develop because of tethering of the lesser curve of the stomach by the gastrohepatic omentum and left gastric vessels.

Type IV is a hernia characterized by displacement of the stomach with other organs, such as the colon, spleen, and small bowel into the chest.



Although this classification is commonly used in the literature and accurately describes the anatomic spectrum of hiatal hernias, from a practical perspective these patients are divided into those with sliding hiatal hernias (type I) and those with PEHs (any one of types II, III, or IV).

The literature on PEHs rarely specifies the type of hiatal hernia with authors typically grouping types II, III, and IV together. Distinguishing between these types of hernias is important, however, because type II usually does not require a gastroplasty, whereas types III or IV hernias may require an esophageal lengthening procedure.[6] For the purposes of this article the focus is primarily on the management of type II to IV hernias, referred to collectively as “paraesophageal” hernias.

Clinical presentation

Although the exact figure is unknown, it is estimated that approximately 50% of patients with PEH are asymptomatic.[5] Confounding the issue is the presence of symptoms that are often nonspecific, minor in severity, and incorrectly ascribed to the “aging process” in this generally elderly patient population. A thorough history often uncovers symptoms related to PEH that were not previously reported on less detailed questioning. When present, symptoms and complications of PEH are reflective of the mechanical alterations caused by the hernia. Broadly, symptoms are either caused by obstruction or by gastroesophageal reflux resulting from a dysfunctional lower esophageal sphincter (LES).

Mechanical obstruction of either the distal esophagus or stomach can result in dysphagia, epigastric pain, vomiting, postprandial fullness, early satiety, or dyspnea. Dysphagia and postprandial discomfort are the most commonly reported symptoms, occurring in more than 50% of symptomatic patients.[7], [8], [9] These symptoms may be minor and episodic, or become severe and unremitting. Occasionally, patients may present with severe epigastric pain caused by incarceration and gastric obstruction. If obstruction persists the stomach distends and ischemia, perforation, and septic shock may ensue. In 1904, Borchardt[10] described a triad of symptoms seen in patients with acute obstruction from PEH that included chest pain, retching with inability to vomit, and inability to pass a nasogastric tube. This rare acute presentation represents a surgical emergency.

Dysfunctional LES resulting from displacement of the stomach into the chest may cause symptoms related to gastroesophageal reflux disease (GERD). Although not as common as symptoms caused by mechanical obstruction, GERD symptoms, such as heartburn, chronic cough, regurgitation, and aspiration, may be reported on careful history.
Important signs associated with PEH are recurrent pneumonia from aspiration and iron deficiency anemia from chronic blood loss. This bleeding may be secondary to esophagitis caused by GERD but more frequently is caused by erosions or ulcerations of the mucosa at an area of gastric folding,[5], [11], [12] called Cameron lesions or ulcers.[13] This anemia resolves in greater than 90% of patients following repair of the hernia.[14], [15]

Evaluation

Evaluation of a patient with a known or suspected PEH depends on the acuity of the presentation and surgeon preference. The goals of the diagnostic evaluation are to establish or confirm the diagnosis of PEH, define the anatomy of the hernia, rule out associated pathologies, and determine the presence or absence of GERD.

Plain chest radiograph often identifies a PEH by revealing a retrocardiac air-fluid level within the intrathoracic stomach. In the acutely unwell patient radiographs may reveal evidence of gastric compromise and perforation manifested as pneumomediastinum or pneumoperitoneum. CT of the chest and abdomen may also provide additional information on the type and location of the hernia.

The most important test in establishing a diagnosis of PEH is the upper gastrointestinal (UGI) series. Key information obtained from this contrast study is the anatomic location of the esophagus and stomach and, more specifically, the position of the GEJ. In some cases, the UGI series reveals complete obstruction caused by gastric volvulus. This radiographic finding indicates a patient requiring urgent surgical intervention.[16]

Endoscopy should be performed on all patients being evaluated for PEH. Esophagoscopy rules out associated pathologies and establishes the diagnosis of PEH while defining the location of the GEJ and the size and type of hernia. In type I hernias, the GEJ and gastric pouch extend above the impression made by the diaphragmatic crura, whereas in a type II hernia there is a separate orifice containing protruded stomach adjacent to a normally located GEJ. A type III hernia may be suspected on endoscopy when a large gastric pouch is seen above the diaphragm with the GEJ entering midway along the side of the pouch. Accurately defining the anatomy of a large hernia may be difficult, however, because of the inability to pass the scope through the stomach and into the antrum.

The use of manometry in the evaluation of PEH is controversial. Proponents of manometry believe that this test allows the LES to be precisely localized resulting in a more accurate classification of the type of hernia.[5], [17] Manometry may also be helpful in assessing the patient for esophageal shortening by measuring the intersphincteric distance between the upper esophageal sphincters and LES.[7] Further, manometry can evaluate the peristaltic function of the esophageal body, which may rule out an undiagnosed motility disorder and the function of the LES, which may assist the surgeon in tailoring an antireflux procedure to a specific patient.[12], [18], [19] Others argue that manometry adds little to the preoperative work-up with other investigations, such as endoscopy and UGI series, able to confirm the diagnosis and classify the type of hernia. Manometry may be technically difficult to perform, with some authors noting an inability to complete the testing in more than 50% of patients with PEH.[18], [19] Finally, preoperative manometric findings do not influence most surgeons' decision to perform an esophageal lengthening procedure or fundoplication when repairing a PEH.

Similarly, ambulatory pH testing in patients with PEH is not usually required[12], [18] because most patients have reflux on pH testing.[20], [21] Most surgeons also routinely perform a fundoplication as part of the PEH repair; pH testing does not alter the planned operation.[22]

Management
In the acute setting, most surgeons agree that urgent surgical intervention is indicated. In the chronic setting there is debate about indications for surgery and the best operative approach. Controversy also exists regarding the need for an esophageal lengthening procedure, fundoplication, fixation of the stomach with gastropexy or gastrostomy, and the need for prosthetic reinforcement of the hiatal closure.

Indications for Surgery

Traditionally, elective surgical repair has been recommended for all patients with PEH considered to be medically operable.[17],[23], [24] Part of the rationale for this recommendation is based on the tendency of PEH to enlarge with time making surgery more difficult and the increasing age of the patient, which may increase the risk of complications. Some surgeons also think that patients with PEH have a high rate of developing lethal complications.[25] In the classic report by Skinner and Belsey[25] 29% (6 of 21) of patients with documented PEH who were observed with minimal symptoms died from complications of strangulation, perforation, or bleeding. In a recent retrospective study by Allen and coworkers[26] 23 of 147 patients were followed after refusing surgery and none of them developed a life-threatening complication of their PEH. Only 4 of these 23 patients ultimately developed progressive symptoms requiring operation. This suggests that a selective approach to surgery is appropriate, with surgery reserved for patients who are symptomatic.[18], [27], [28] Some surgeons believe that emergency repair of PEH is associated with a high mortality rate. In 1973, Hill[29] reported a series of patients with acute gastric volvulus associated with PEH that had an operative mortality rate of 56%. This high mortality rate provided further impetus to repair all PEH regardless of symptoms. Several recent reports, however, including a pooled analysis by Stylopoulos and coworkers,[28] demonstrate a much lower mortality rate (5%–17%) for emergency surgery.[30], [31], [32], [33], [34], [35] In light of this information, it seems reasonable that asymptomatic or minimally symptomatic patients do not necessarily require surgery and that a more selective approach should be used.[36], [37], [38] There remains little debate, however, that all symptomatic patients who are a good surgical risk should be repaired.[38], [39]

Approach to Surgery

The three approaches for repair of PEH are (1) transthoracic, (2) transabdominal, and (3) laparoscopic. Regardless of the approach, the tenets for a successful repair of PEH are tension-free reduction of hernia contents into the subdiaphragmatic position, removal of the hernia sac, and closure of the hiatal defect.[40] Most surgeons also agree that performing an antireflux procedure is an important element of a successful PEH repair. The role of fixation of the stomach below the diaphragm with gastropexy or gastrostomy is debated.

Traditionally, PEH repair was through a thoracotomy or laparotomy. Proponents of the thoracic approach emphasized the ease of dissection of the hernia sac and its contents and the enhanced ability to fully mobilize the esophagus to reduce tension and minimize the need for a lengthening procedure. If a lengthening procedure is required, it is generally easier with the thoracic approach. The thoracic repair has the disadvantages of being associated with increased pain and pulmonary complications postoperatively, the need for tube thoracostomy, increased hospital stay and cost, and the potential for volvulus after reduction of the stomach into the abdomen.[40], [41], [42]

Advocates of the abdominal approach argue that it permits complete mobilization of the stomach with improved reduction of the volvulus and recreation of the normal anatomy. This approach also allows other abdominal procedures, such as gastropexy or gastrostomy, to be performed. Mobilization of the distal esophagus can be challenging, however, making gastroplasty for esophageal shortening more difficult to perform.[42]

There are no randomized studies comparing open abdominal with thoracic approaches in the repair of PEH. Table1 lists the outcomes of several studies of PEH repair using either technique.[7], [27], [33], [43], [44], [45], [46], [47], [48], [49] Comparing these series is difficult because of variable clinical and radiographic follow-up and different and inconsistent outcome measures. Low and Unger[48] report the highest rate of recurrence (18%) with most recurrences being asymptomatic. This result likely represents a true estimate of anatomic recurrence based on the thorough follow-up investigations performed by the authors. Despite these differences, these studies indicate that both transthoracic and transabdominal approaches have good outcomes with low postoperative mortality rates and acceptable rates of recurrence.

Table 1. Outcomes of selected series of open thoracic and abdominal repair of PEH

	References	Year	N	% Lengthening Gastroplasty	% Good or Excellent Results	% Anatomic Recurrence	Follow-up (Months)
Transthoracic repair	Allen et al26	1993	124	68	93	NR	42 (median)
	Maziak et al7	1998	94	80	94	2	72 (median)
	Altorki et al44	1998	47	0	91	6	45 (median)
	Patel et al45	2004	240	96	85	8	42 (median)
Transabdominal repair	Williamson et al46	1993	119	1	84	11	61 (median)
	Myers et al47	1995	37	0	92	0.3	67 (median)
	Low and Unger48	2005	72	0	NR	18	30 (mean)
Mixed series	Martin et al49	1997	51	NR	86	4	27 (mean)
	Geha et al33	2000	100	2	98	0	NR

The first report of laparoscopic repair of PEH was published in 1992.[50] Today there is far more published literature on minimally invasive repair of PEH than on all the open series combined. Advocates of the laparoscopic approach claim that it has decreased postoperative morbidity and affords superior visualization of the hiatus and mediastinum, which allows better distal esophageal mobilization.[22], [42] Arguments against this approach include the advanced laparoscopic skills required to perform the surgery, the lack of long-term follow-up, and a higher recurrence rate of PEH.[22], [40] There are no randomized control trials comparing laparoscopic with open PEH repair to support these claims. Scieman and Grondin published the short-term outcomes of primary laparoscopic and open PEH repairs in 93 patients.[51] The primary outcome measures included intraoperative parameters, such as operative time, and postoperative variables, such as hospital stay and complications. Secondary outcomes included mortality rates, recurrence rates, and patient satisfaction. It was concluded that the laparoscopic approach was associated with a significantly longer operative time (3.1 hours) compared with the open procedure (2.5 hours). The overall hospital stay was shorter in the laparoscopic group (5 days), however, compared with the open repair group (10 days) and was associated with fewer postoperative complications. Although the follow-up was short (average 17 months), the patient satisfaction scores and recurrence rates (9%) were similar in both groups.

Table 2 lists the outcomes of several studies using the laparoscopic approach for repair of PEH.[52], [53], [54], [55], [56], [57], [58], [59]

Advocates of the minimally invasive approach cite series that demonstrate decreased length of stay, lower postoperative complication rates, and lower mortality rates than the open repair. In a review of 32 different case series, Draaisma and coworkers[24] reported a lower perioperative complication rate and a shorter mean length of stay for the laparoscopic versus the open group (3 versus 10 days). Rathore and coworkers[60] published a meta-analysis of nonrandomized series on laparoscopic PEH repair. Inclusion was restricted to those series with greater than 25 patients and follow-up beyond 6 months. In 965 patients the overall recurrence rate was 10.2%. Among those patients formally evaluated with a contrast esophagogram postoperatively 25.5% had recurrence. Lower recurrence rates were seen in those who underwent an esophageal lengthening procedure with a Collis-Nissen gastroplasty versus those who did not (0% vs 12%). Despite both the widespread adoption of laparoscopic techniques for various procedures and the impressive published results, laparoscopic repair of PEH has not been universally adopted. In a recent international online survey of members of the Cardiothoracic Surgery Network only 48% stated they repair PEH laparoscopically, whereas 35% perform thoracotomy and 17% perform laparotomy.[61]

Table 2. Outcomes of selected series of laparoscopic repair of PEH

Author	Year	N	% Lengthening Gastroplasty	% Anatomic Recurrence	Follow-up (Months)
Trus et al52	1997	76	8	11	15 (median)
Wiechmann et al53	2001	60	0	7	40 (mean)
Mattar et al54	2002	136	5	43	18 (median)
Pierre et al55	2002	203	56	2	37 (mean)
Jobe et al56	2002	52	0	32	37 (mean)
Diaz et al57	2003	116	5	32	30 (mean)
Andujar et al58	2004	166	0	5	15 (mean)
Boushey et al59	2008	58	0	9	6 (mean)

The debate surrounding the best surgical approach for repairing PEH continues with several studies reporting that each approach can be performed safely with acceptable outcomes.

Esophageal Shortening

The true incidence of esophageal shortening in PEH is unknown and remains a major point of controversy. Despite having been described for over 50 years,[62] questions remain as to the existence and the management of a shortened esophagus. Those who believe that shortening does not exist argue that in most patients the esophagus appears shortened because the stomach is pushing it up into the chest. Correction of the anatomic arrangement avoids the need for a lengthening procedure.[63] A more commonly held view is that although short esophagus is uncommon, it remains an important cause of recurrence following PEH repair.[18], [64] Inadequate esophageal length limits the ability to reduce the GEJ into its normal abdominal position without tension, which predisposes to wrap herniation and anatomic recurrence.[64]

The most important risk factor for esophageal shortening is the presence of periesophageal inflammation resulting from long-standing GERD.[64] It is thought that GERD leads to chronic irritation followed by healing and subsequent fibrosis.[65] Studies of patients diagnosed with GERD demonstrate a wide range of incidence of short esophagus (0%–60%).[66], [67], [68] Other risk factors that may predispose a patient to develop esophageal shortening include Barrett esophagus, scleroderma, and Crohn disease.[65], [68]

Identifying patients preoperatively with shortened esophagus is problematic.[69], [70] There is no test that can be performed that accurately identifies the presence and degree of esophageal shortening. Several techniques have been described using endoscopic or radiologic measurements of length and manometric measurements.[70], [71], [72], [73] Unfortunately, none of these are completely reliable at predicting a shortened esophagus intraoperatively.[70], [74], [75] The most reliable method of determining esophageal shortening is intraoperative assessment (eg, GEJ >2.5 cm below the hiatus).[64], [75]

When a diagnosis of short esophagus is made a lengthening procedure is necessary. This may be accomplished by further intrathoracic dissection and mobilization of the esophagus or by gastroplasty. In 1957, Collis[76] described this procedure without fundoplication. Subsequently, fundoplication was added to prevent reflux and is referred to as Collis-Nissen.[77] Although a Collis-Nissen is most easily done by thoracotomy, it can be performed through any approach.[78], [79] There is general agreement that a lengthening gastroplasty reduces the rate of recurrent herniation following repair of PEH when esophageal shortening is observed.[6], [43]

Esophageal shortening is less commonly identified in patients undergoing laparoscopic repair of PEH.[22] This observation may be related to difficulty in accurately identifying the GEJ because of

inadequate removal of the fat pad, elevation of the diaphragm from insufflation of carbon dioxide, or improved distal esophageal mobilization.[6] Some surgeons may also be reluctant to perform a gastroplasty using laparoscopic techniques because of technical challenges. Long-term follow-up of patients undergoing laparoscopic repair of PEH is necessary to determine if decreased use of gastroplasty in the laparoscopic approach results in higher recurrence rates.

Antireflux Procedure

Although limited data confirm the need for fundoplication, most surgeons perform an antireflux procedure when repairing a PEH[24] because the fundoplication helps to anchor the stomach in the abdomen and because of the need to recreate a barrier to reflux. The extensive dissection necessary for full mobilization of the hernia sac and esophagus completely disrupts the hiatal mechanism and may render the GEJ incompetent resulting in postoperative reflux. An incidence of postoperative reflux as high as 65% in patients who did not receive a fundoplication has been reported.[37], [63], [80] These results have been disputed and a few argue that significant postoperative reflux is much less common in patients without fundoplication and, if present, can be managed with medical therapy.[46] Some authors believe that avoiding a fundoplication decreases the risk of postoperative dysphagia and operative complications, and shortens the operative time for patients who are often elderly with significant medical comorbidities.[81] These authors suggest that fundoplication should be performed selectively in patients diagnosed with GERD on preoperative evaluation.

Fixation of the Stomach with Gastropexy or Gastrostomy

In many patients, reherniation occurs because of positive intra-abdominal pressure and negative intrathoracic pressure creating a cephalad force that favors migration of the stomach into the thorax. By anchoring the stomach below the diaphragm by gastropexy or gastrostomy, it is hoped that this migration is avoided.[63] Surgeons who argue for gastropexy note that it is fast and simple to perform; however, a high rate of recurrence has been reported using this technique.[22], [82], [83] Those who favor gastrostomy argue that it provides a solid anchoring point to prevent recurrence and decreases the risk of intra-abdominal gastric volvulus.[22] Gastrostomy also effectively decompresses the stomach and eliminates the need for a nasogastric tube postoperatively. Those surgeons who oppose fixation of the stomach report that reherniation is not prevented because the stomach is pliable and merely stretches in response to the cephalad force.[22] No prospective randomized study has been reported that proves that either of these two techniques reduces the rate of recurrence.

Mesh Reinforcement of the Crural Repair

PEH repair is often complicated by excessive tension of the hiatal closure, attenuated crura with poor quality tissue, and unrecognized esophageal shortening. These factors predispose the crural repair to disruption and lead to reherniation. To improve the strength of the crural repair, surgeons have used prosthetic mesh. This approach is supported by the successful use of mesh for the repair of inguinal and incisional hernias. In these patients, the mesh causes secondary in-growth and fibrosis and significantly reduces the incidence of hernia recurrence.[84], [85], [86]

Data supporting the use of prosthetics for crural reinforcement during PEH repair are limited because most studies are small observational case series using different techniques of repair and different prosthetic materials.[87] Three techniques for mesh placement have been described with each intended to provide mechanical support to the hiatal closure: (1) primary closure of the crura followed by prosthetic onlay,[88] (2) the “keyhole” technique whereby a slit and hole are cut into the mesh and it is placed around the esophagus onto the crura,[89] and (3) the “tension free” repair whereby the hiatal defect is left open and mesh is used to bridge the gap between the crura.[90]

Prosthetic insertion may cause complications including erosion into the esophagus, adhesions, fibrotic strictures, and dysphagia.[91], [92], [93], [94] Prosthetic erosion is rare but catastrophic and may require esophagectomy as definitive management.[88], [91], [92], [93], [94] To address these concerns, biologic mesh, such as porcine small intestinal submucosa and acellular human dermis, have been investigated.[22], [40] Theoretically, these materials are safer because they act as infection-resistant temporary scaffolding that allows for native tissue in-growth without the degree of scarring created by synthetic mesh.[95], [96]

Despite the drawbacks listed previously, there is increasing evidence[90, 97, 98, 99] including two prospective randomized controlled trials[88, 89] suggesting that mesh reinforcement of crural closure decreases the risk of reherniation (Table 3). Oelschlager and coworkers[100] demonstrated similar results using bioprosthetic mesh with no mesh-related complications reported. Long-term follow-up is required to ensure that erosion into the esophagus does not occur with newer materials.

Table 3. Outcomes of selected series of laparoscopic repair of PEH with mesh prosthesis

	References	Year	N	% Recurrence	Prosthetic Material	Placement of Mesh	Follow-up (Months)
Non-randomized trials	Basso et al 90	2000	65 NM 70 M	14 0	PP	Tension free	23
	Hui et al97	2001	12 NM 12 M	0 8	PTFE	Onlay	37
	Champion and Rock 98	2003	52 M	2	PP	Onlay	25
	Keidar and Szold99	2003	23 NM 10 M	17 10	Composite	Keyhole	58
Randomized trials	Frantzides et al89	2002	36 NM 36 M	23 0	PTFE	Keyhole	40
	Granderath et al88	2005	50 NM 50 M	26 8	PP	Onlay	12
	Oelschlager et al100	2006	57 NM 51 SM	24 9	Porcine SIS	Onlay	6

Abbreviations: M, mesh; NM, no mesh; PP, polypropylene; PTFE, polytetrafluoroethylene; SIS, small intestinal submucosa; SM, synthetic mesh

Summary

Practically, hiatal hernias are divided into sliding hiatal hernias (type I) and PEH (types II, III, or IV). Patients with PEH are usually symptomatic with GERD or obstructive symptoms, such as dysphagia. Rarely, patients present with acute symptoms of hernia incarceration, such as severe epigastric pain and retching. A thorough evaluation includes a complete history and physical examination, chest radiograph, UGI series, esophagogastroscopy, and manometry. These investigations define the patient's anatomy, rule out other disease processes, and confirm the diagnosis. Operable symptomatic patients with PEH should be repaired. The underlying surgical principles for successful repair include reduction of hernia contents, removal of the hernia sac, closure of the hiatal defect, and an antireflux procedure. Debate remains whether a transthoracic, transabdominal, or laparoscopic approach is best with good surgical outcomes being reported with all three techniques. Placement of mesh to buttress the hiatal closure is reported to reduce hernia recurrence. Long-term follow-up is required to determine whether the laparoscopic approach with mesh hiatoplasty becomes the procedure of choice.

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Salivary Gland Tumors

Sushanto Neogi

Salivary glands are exocrine organs responsible for the production and secretion of saliva. They comprise the three paired major glands, the parotid, submandibular and sublingual, and the minor glands.

Epidemiology

The reported incidence of all salivary gland tumors in literature is reported 0.4 to 13.5 per 100000 population. The incidence of malignant tumors ranged from 0.4 to 2.6 per 100000 population. Almost 60 to 80% of tumors are in the parotid gland, around 2% to 10% in submandibular and sublingual gland and 9 to 20% in the minor salivary glands.[1]

Out of these 60-80% are benign and 20-40 % are malignant. Depending upon the site also the risk of malignancy changes, e.g. 80% of parotid tumors are benign, whereas around 40 to45% of submandibular tumors are malignant. This approaches almost 90% in case of sublindual and 59% for minor salivary gland tumors.

Average age of benign tumors is 40 years and peak incidence of most malignant tumors is after 5^{th} to 6^{th} decade. Females are more commonly affected than males, though in case of individual tumors this relationship changes.[1]

The most common tumor type is pleomorphic adenoma followed by Warthins tumor. Mucoepidermoid carcinoma is the most common malignancy.[1]

Etiology

1. Viruses- Epstein Barr and papiloma viruses have been implicated but till now no definite association has been proven.
2. Radiation- Exposure to ionizing radiation has been implicated for development of both benign and malignant salivary gland tumors. Survivors of Japanese atomic bombings have shown and increase in 3.5% increase in benign ad 11% of malignant salivary tumors. Therapeutic radiation to head and neck region is linked to high risk of developing salivary gland tumors. Same is true for radioactive iodine therapy used for thyroid ablation as radioactive iodine gets concentrated in salivary glands also.
3. Occupation- people working in rubber manufacturing industry, plumbing industry, wood workers etc, are more prone to develop salivary gland tumors.
4. Smoking- there is a strong association between Warthin's tumor and smoking.[2]

Anatomical considerations

Parotid gland

The parotid gland is the largest of the salivary glands. It is located in a compartment anterior to the ear and is invested by fascia that suspends the gland from the zygomatic arch. The parotid compartment contains the parotid gland, nerves, blood vessels, and lymphatic vessels, along with the gland itself.

The compartment may be divided into superficial and deep portions, but the space has no discrete anatomic divisions. The superficial portion contains the facial nerve, great auricular nerve, and auriculotemporal nerve. The deep portion contains the superficial temporal vein, which unites with the internal maxillary vein to form the posterior facial vein.

The parotid compartment is a wedge-shaped 3-dimensional area with superior, anterior diagonal, posterior diagonal, and deep borders. It is bounded superiorly by the zygomatic arch; anteriorly by the masseter muscle, lateral pterygoid muscle, and mandibular ramus; and inferiorly by the sternocleidomastoid muscle and the posterior belly of the digastric muscle. The deep portion lies lateral to the parapharyngeal space, styloid process, stylomandibular ligament, and carotid sheath.

The deep anatomic relationship is important because tumors may arise in the deep portion and grow into the parapharyngeal space and may manifest as intraoral masses. These tumors are termed dumbbell tumors when they grow between the posterior aspect of the mandibular ramus and the stylomandibular ligament. This position causes a narrow constricted portion with larger unrestricted portions on either side, forming a dumbbell shape.

The parotid is a unilobular gland through which the facial nerve passes. No true superficial and deep lobes exist. The term superficial parotidectomy or parotid lobectomy refers only to the surgically created boundary from facial nerve dissection.

The Stensen duct drains the parotid gland. Initially, it is located approximately 1 cm below the zygoma and runs horizontally. It passes anteriorly to the masseter muscle and then penetrates the buccinator muscle to open intraorally opposite the second maxillary molar.

The facial nerve exits the skull via the stylomastoid foramen located immediately posterior to the base of the styloid process and anterior to the attachment of the digastric muscle to the mastoid tip at the digastric ridge. The nerve travels anteriorly and laterally to enter the parotid gland. Branches of the facial nerve that innervate the posterior auricular muscle, posterior digastric muscle, and stylohyoid muscle arise before the nerve enters the parotid gland. Just after entering the parotid gland, it divides into 2 major divisions: the upper and lower divisions. This branch point is referred to as the pes anserinus. Subsequent branching is variable, but the nerve generally forms 5 branches. The buccal, marginal mandibular, and cervical branches arise from the lower division. The zygomatic and temporal branches arise from the upper division.

Branches of the external carotid artery provide arterial supply to the parotid gland. The posterior facial vein provides venous drainage, and lymphatic drainage is from lymph nodes within and external to the gland that leads to the deep jugular lymphatic chain.

The gland receives parasympathetic secretomotor innervation from preganglionic fibers that arise in the inferior salivatory nucleus. These fibers travel with the glossopharyngeal nerve to exit the skull via the jugular foramen. They then leave the glossopharyngeal nerve as the Jacobson nerve and reenter the skull via the inferior tympanic canaliculus. The fibers traverse the middle ear space broadly over the promontory of the cochlea (tympanic plexus) and exit the temporal bone superiorly as the lesser petrosal nerve. The lesser petrosal nerve exits the middle cranial fossa through the foramen ovale, where the preganglionic fibers synapse in the otic ganglion. The postganglionic fibers travel with the auriculotemporal nerve to supply the parotid gland.[2]

Submandibular gland

The submandibular glands are the second largest salivary glands, after the parotid. They are encapsulated glands located anterior and inferior to the angle of the mandible in the submandibular triangle formed from the anterior and posterior bellies of the digastric muscle and the inferior border of the mandible.

The submandibular gland has a superficial portion located lateral to the mylohyoid and a deep portion located between the mylohyoid and the hyoglossus. The marginal mandibular branch of the facial nerve and the anterior facial vein pass superficially to the gland. Posteriorly, the gland is separated from the parotid gland by the stylomandibular ligament. The facial artery crosses the deep portion of the gland.

The Wharton duct drains the gland. It passes between the mylohyoid and hyoglossus muscles and along the genioglossus muscle to enter the oral cavity lateral to the lingual frenulum.

The lingual nerve and submandibular ganglion are located superior to the submandibular gland and deep to the mylohyoid muscle. The hypoglossal nerve lies deep to the gland and inferior to the Wharton duct.

Arterial blood supply is from the lingual and facial arteries. The anterior facial vein provides venous drainage. The lymphatic drainage is to the submandibular nodes and then to the deep jugular chain.

The submandibular and sublingual glands receive parasympathetic secretomotor innervation from preganglionic fibers, which originate in the superior salivatory nucleus. These fibers leave the brainstem as the nervus intermedius to join with the facial nerve. They then leave the facial nerve with the chorda tympani to synapse in the submandibular ganglion. Postganglionic fibers innervate the submandibular and sublingual glands.[2]

Sublingual glands

The sublingual glands are the smallest of the major salivary glands. Unlike the parotid and submandibular gland, the sublingual gland is unencapsulated. Each gland lies medial to the mandibular body, just above the mylohyoid muscle and deep to the mucosa of the mouth floor.

Rather than 1 major duct, the sublingual glands have 8-20 small ducts, which penetrate the floor of mouth mucosa to enter the oral cavity laterally and posteriorly to the Wharton duct. Arterial supply is from the lingual artery. Lymphatic drainage is to the submental and submandibular lymph nodes, then to the deep cervical lymph nodes. Innervation is via the same pathway as the submandibular gland.[2]

Minor salivary glands

Approximately 600-1000 minor salivary glands are located throughout the paranasal sinuses, nasal cavity, oral mucosa, hard palate, soft palate, pharynx, and larynx. Each gland is a discrete unit with its own duct opening into the oral cavity.

Together, the salivary glands produce 1-1.5 L of saliva per day. About 45% is produced by the parotid gland, 45% by the submandibular glands, and 5% each by the sublingual and minor salivary glands. Saliva is produced at a low basal rate throughout the day, with a 10-fold increase in flow during meals. Saliva functions to maintain lubrication of the mucous membranes and to clear food, cellular debris, and bacteria from the oral cavity. Saliva contains salivary amylase, which assists in initial digestion of food. Saliva forms a protective film for the teeth and prevents dental caries and enamel

breakdown, which occur in the absence of saliva. Also, by virtue of production of lysozyme and immunoglobulin A in the salivary glands, saliva plays an antimicrobial role against bacteria and viruses in the oral cavity.[2]

Presentation

Benign tumors present as slow growing swellings in the anatomical locations of the respective glands. Few of the malignant tumors can have a slow progression but malignant tumors are usually marked by their rapid progression. Associated pain is a poor prognostic sign. Involvement of the surrounding nerves is hall mark of malignant infiltration by the tumors.

Clinical examination

Along with the site, the clinician is concerned about which lobe the tumor is arising from (Superficial or deep) for parotid tumors. Whether it is benign or malignant, fixity to the deeper structures, involvement of facial nerve, etc should be elicited. The size, mobility, and extent of the mass, as well as its fixation to surrounding structures and any tenderness should be noted. Bimanual palpation of the lateral pharyngeal wall for deep lobe parotid tumors to assess for parapharyngeal space extension should be done. Bimanual palpation for submandibular and sublingual masses also reveals the extent of the mass and its fixation to surrounding structures.

The surrounding skin and mucosal sites, which drain to the parotid and submandibular lymphatics should be properly examined. The opening of the ducts of major salivary glands are fixed, these should be examined for any discharge or inflammation. Also, the cervical lymph node basin should be palpated to assess for metastatic disease from a primary lesion of the salivary glands.

Cranial Nerve VII should be assessed carefully to identify any weakness or paralysis. Facial nerve palsy usually indicates a malignant lesion with infiltration into the nerve.[3]

Investigations

Fine Needle Aspiration Cytology
Most of the benign tumors do not require many investigations other than Fine needle aspiration cytology (FNAC). Fine needle aspiration biopsy (FNA), operated in experienced hands, can determine whether the tumor is malignant in nature with sensitivity around 90%.[4,5] FNA can also distinguish primary salivary tumor from metastatic disease. If required fine needle core biopsy may be done for confirmation. It is more invasive but is more accurate compared to FNA with diagnostic accuracy greater than 97%.[6]

Ultrasonography
New technologies, including high-resolution probes and harmonic imaging, can delineate location, homogeneity or heterogeneity, shape, vascularity, and margins of salivary tumors in the periauricular, buccal, and submandibular area.

Ultrasonography may be able to reveal the type of tumor. New ultrasonographic contrast mediums can now reveal the vascularity of the tumor before surgery. Ultrasonography can guide fine-needle aspiration to increase the likelihood of getting a good sample, and it can precisely guide core needle biopsies 97% of the time in an outpatient setting, lessening the need for intraoperative biopsies. Ultrasonography can also guide automated core biopsy systems with a sensitivity of 75%, specificity of 96.6%, and accuracy of 91.9%.[6,7]

Computer Tomography (CT) scanning and Magnetic Resonance Imaging (MRI)
Imaging studies of the salivary glands are usually unnecessary for the assessment of small tumors, especially benign, within the parotid or submandibular gland. CT scanning or MRI is useful for determining the extent of large tumors, for evaluating extraglandular extension, for determining the actual depth of parotid tumors, and for discovering other tumors in one gland or in the contralateral gland. Additionally, CT scanning and MRI are helpful in distinguishing an intraparotid deep-lobe tumor from a parapharyngeal space tumor and for evaluation of cervical lymph nodes for metastasis.[8,9]

CT scanning and MRI can be used to predict possible malignancy based on observation of poorly defined tumor margins; MRI is the better of the two for this purpose. However, no difference exists between the specificities and sensitivities of CT scanning and MRI for the location or amount of infiltration of tumors in the parotid gland.[8,9]

Minor salivary gland neoplasms are often difficult to assess on examination and the use of preoperative CT scanning or MRI is important for determining the extent of tumor, which is otherwise not clinically appreciable. This imaging is particularly valuable for salivary gland neoplasms in the paranasal sinus, where skull-base or intracranial extension may alter the resectability of the tumors.

CT-guided needle biopsy can be used to evaluate difficult-to-reach tumors, such as neoplasms in the parapharyngeal space.

For most small parotid neoplasms without clinical evidence of facial nerve involvement, no pretreatment imaging studies are required.

Gadolinium-enhanced dynamic MRI can be used to possibly differentiate pleomorphic adenomas from malignant salivary gland tumors using peak time of enhancement at 120 seconds and to differentiate between malignancies and Warthin tumors using washout ratios of 30% with a sensitivity of 100% and specificity of 80%. However, MRI can only suggest a diagnosis; definitive diagnosis requires pathologic examination.

CT is excellent for demonstrating bony invasion. MRI provides superior soft tissue delineation such as perineural invasion when compared to CT only.[9,10]

Nuclear imaging

F-18 fluorodeoxyglucose (FDG)-PET can be used to plan treatment of salivary gland malignancies by detecting lymph node metastases that require a neck dissection or by finding distant metastases that may not have caused abnormalities in routine blood work. This is most useful when combined with CT scanning.

Technetium-99m (Tc-99m) pertechnetate scintigraphy with lemon juice stimulation can be used to diagnose Warthin tumors with correlation between tumor size and Tc-99m uptake.[10]

Various classifications of salivary gland tumors but for universal uniformity, WHO based classification is widely accepted.

2005 WHO classification of epithelial Salivary Gland Tumors.[3]

Benign epithelial tumors
Pleomorphic adenoma
Myoepithelioma
Basal cell adenoma
Warthin tumor
Oncocytoma
Canalicular adenoma
Sebaceous adenoma
Lymphadenoma
Ductal papilloma
Cystadenoma

Malignant epithelial tumors
Acinic cell carcinoma
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Polymorphous low-grade adenocarcinoma
Epithelial-myoepithelial carcinoma
Clear cell carcinoma, not otherwise specified
Basal cell adenocarcinoma
Malignant sebaceous tumors
Cystadenocarcinoma
Low-grade cribriform cystadenocarcinoma
Mucinous adenocarcinoma
Oncocytic carcinoma
Salivary duct carcinoma
Adenocarcinoma, not otherwise specified
Myoepithelial carcinoma
Carcinoma ex pleomorphic adenoma
Carcinosarcoma
Metastasizing pleomorphic adenoma
Squamous cell carcinoma
Small cell carcinoma
Large cell carcinoma
Lymphoepithelial carcinoma
Sialoblastoma

The salivary gland malignancies have further been classified as low risk and high risk groups based on similarities of their growth patterns, resectabilty, recurrence rates, metastatic rates and 5 year survival rates.

Risk stratification of WHO recognized salivary gland malignancies.[3]

Low risk	High risk
Acinic cell carcinoma	Sebaceous and lymphadenocarcinoma
Low grade mucoepidermoid carcinoma	High grade mucoepidermoid carcinoma
Epithelial-myoepithelial carcinoma	Adenoid cystic carcinoma
Polymorphous low grade adenocarcinoma	Mucinous adenocarcinoma
Clear cell carcinoma	Squamous cell carcinoma
Basal cell adenocarcinoma	Small cell carcinoma
Low grade salivary duct carcinoma (low grade cribriform cystadenocarcinoma)	Large cell carcinoma
Myoepithelial carcinoma	Lymphoepithelial carcinoma
Oncocytic carcinoma	Metastasizing pleomorphic adenoma
Carcinoma ex pleomorphic adenoma (intracapsular/minimally invasive or with low grade histology)	Carcinoma ex pleomorphic adenoma (widely invasive or high grade histology)
Sialoblastoma	Carcinosarcoma
Adenocarcinoma NOS and Cystadenocarcinoma, low grade	Adenocarcinoma and Cystadenocarcinoma, NOS,

Malignant salivary gland tumours are staged using the TNM staging system:[20]

Table. TNM classification[20]

Primary tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ

T1 Tumor =2cm in greatest dimension without extraparenchymal extension (clinical or macroscopic evidence of invasion of the soft tissues, not microscopic evidence)

T2 Tumor >2cm but not more than 4cm in greatest dimension without extraparenchymal extension

T3 Tumor >4cm and/or tumor has extraparenchymal extension

T4a Moderately advanced disease
- Tumor invades the skin, mandible, ear canal, and/or facial nerve

T4b Very advanced disease
- Tumor invades skull base and/or pterygoid plates and/or encases carotid artery

Regional lymph nodes (N)

NX Regional nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single ipsilateral lymph node =3cm in greatest dimension

N2 Metastasis in a single ipsilateral lymph node >3cm but not more than 6cm in greatest dimension; or in multiple ipsilateral lymph nodes, none >6cm in greatest dimension; or in bilateral or contralateral lymph nodes, none >6cm in greatest dimension

N2a Metastasis in a single ipsilateral lymph node >3cm but not more than 6cm in greatest dimension

N2b Metastasis in multiple ipsilateral lymph nodes, none >6cm in greatest dimension

N2c Metastasis in bilateral or contralateral lymph nodes, none >6cm in greatest dimension

N3 Metastasis in a lymph node >6cm in greatest dimension

Distant metastasis (M)

M0 No distant metastasis

M1 Distant metastasis

Treatment

Surgery
Surgery in form of complete excision,(superficial parotridectomy, total parotidectomy {removal of both superficial and deep lobes} surgery for benign parotid tumors) for benign salivary tumors is sufficient for treatment.

For malignant tumors of parotid radical parotidectomy {total parotidectomy along with facial nerve excision and/or modified or radical neck dissection} is the trreatnent of choice for resectable tumors. . For other tumors, wide excision with or without radical lymph node dissection, if amenable to excision is the surgical option.

Chemotherapy
In general, salivary gland neoplasms respond poorly to chemotherapy, and adjuvant chemotherapy is currently indicated only for palliation. Doxorubicin- and platinum-based agents are most commonly used with the platinum-based agents that induce apoptosis versus the doxorubicin-based drugs that promote cell arrest. Platinum-based agents, in combination with mitoxantrone or vinorelbine, are also effective in controlling recurrent salivary gland malignancy. A new form of 5-fluorouracil called fluoropyrimidine that has increased activity against malignant cells and while having fewer gastrointestinal side effects has shown to be efficacious against malignant salivary cancers and to potentiate the effects of radiotherapy by increasing apoptosis.

Newer trials with antimicrotubule agents with and without concomitant radiotherapy have shown efficacy. Using a platinum-based agent, cisplatin, and an antimicrotubule drug, docetaxel, with radiation shows some promise in advanced carcinomas of the salivary gland. Using paclitaxel, another antimicrotubule drug, alone has had moderate activity against mucoepidermoid tumors and adenocarcinomas but no effect adenoid cystic carcinoma.

Various targeted biologic agents such as trastuzumab, imatinib, and cetuximab are currently being investigated.[11]

Radiotherapy
Radiotherapy is still not considered to be the criterion standard after surgical resection of salivary gland neoplasms; however, it is used alone for tumors that are considered nonresectable. More studies have quantified the use of radiotherapy in the postoperative setting. The use of radiation in T1 and T2 parotid gland tumors found that 5-year disease-free survival increased from 70% to 92% with postoperative radiation. A second study investigated postresection radiotherapy for carcinoma ex pleomorphic adenoma and found a 26% improvement in 5-year local control (from 49% to 75%). Nonetheless, prospective randomized controlled studies are needed to confirm the usefulness of postoperative radiotherapy.

Newer techniques for postoperative radiation in salivary gland malignancies have been proven effective. These include gamma-knife stereotactic radiosurgery and brachytherapy (radioactive seeds or sources are placed in or near the tumor itself, giving a high radiation dose to the tumor while reducing the radiation exposure in the surrounding healthy tissues). Iodine-125 seeds have been found to be an effective treatment for incompletely resected or unfavorable histological salivary gland malignancies of the hard and soft palate. Gamma-knife treatments after neutron therapy are useful if the local failure risk is still high.

Recent reports have shown that neutron-based radiation therapy may be more effective than photon-based radiation therapy for the treatment of malignant salivary gland neoplasms with gross disease and provides excellent local and regional control of microscopic disease. This therapy has been proven to have good local control and survival rates in patients with grossly recurrent pleomorphic adenomas that cannot be resected. In adenoid cystic carcinoma that is recurrent, is advanced, or has been resected with positive margins, neutron therapy can provide better local control than photon-based therapies, but it does not improve survival because of the excessive number of metastases that prevail in advanced stages. Doses as high as of 60 Gy (1 Gy=100 rad) were needed in stage 3 or 4 tumors that have invaded bone, nerves, or lymph nodes. If the tumor is completely unresectable, doses as high as 66 Gy are needed.[11]

Description of common salivary gland tumors[12,13]

Pleomorhic adenoma
It is the commonest tumor of salivary glands. Parotid 84%, submandibular gland - 8%,minor salivary glands - 6.5%, sublingual glands-0.5%

Epidemiology
The tumor occurs most frequently in the fifth decade and shows a slight female preponderance.

Pathology
It is a benign tumor with a mixture of cellular and myxoid combination giving its morphological diversity. It comprises epithelial and myoepithelial cells variably arranged in a mucoid, myxoid or chondroid background. Epithelial cell types observed in PA include cuboidal, basaloid, squamous, clear, and spindle cells. The mesenchymal tissue is mucoid, myxoid or chondroid, and the reason for the synonym mixed parotid tumor. The tumor is not enveloped, but it is surrounded by a fibrous pseudocapsule of varying thickness. The tumor extends through normal glandular parenchyma in the form of finger-like pseudopodia, but this is not a sign of malignant transformation.

Clinical features
It is a painless slow growing benign tumor, located commonly in the superficial lobe of the parotid gland. It can grow to large sizes over several years without causing much symptoms. Very rarely the facial nerve can be involved by direct compression of the nerve by the size of the tumor. More commonly the facial nerve gets involved when they undergo malignant transformation, to form carcinoma ex-pleomorphic adenoma, a risk that increases with time (9.5% chance to convert into malignancy in 15 years). This involvement is a direct infiltration and in all cases of facial nerve involvement in pleomorphic adenoma the diagnosis should be a malignant transformation unless proved otherwise. Although it is "benign" the tumor is aneuploid, it can recur after resection, as it invades normal adjacent tissue and does not have a true capsule. Distant metastases have been reported after long (+10 years) time intervals.

Examination shows a pyramidal swelling in the region of tail of parotid gland which usually lifts the lobule of the ear. The gland shows a bosselated surface and if the superficial lobe is involved, it is slightly mobile. Most of the time a single nodule gets enlarged rather than the tumor becoming multinodular. Pleomorphic adenoma in the deep lobe of the parotid gland may present as an oral retrotonsillar mass or parapharyngeal space tumor.

Treatment
Surgical excision is curative, however as the tumour is poorly encapsulated. Superficial parotidectomy is the minimal surgery to be performed. Earlier enucleation was done and patients had a recurrence rate to the tune of 20-45%.[14]

Warthin's tumor or **Warthin tumour**
Also known as papillary cystadenoma lymphomatosum, monomorphic adenoma or adenolymphoma, is benign cystic tumor of the salivary glands containing abundant lymphocytes and germinal centers (lymph node-like stroma). It is named for pathologist Aldred Scott Warthin, who described two cases in 1929.[1]

Its etiology is unknown, but there is a strong association with cigarette smoking. Smokers are at eight times greater risk of developing Warthin's tumor than the general population. Warthin's tumor is the only tumor virtually restricted to the parotid gland. It is the second most common benign parotid tumor.[15,16]

Epidemiology
Warthin's tumor primarily affects older individuals (age 60–70 years). Historically it has been associated with a strong male predilection, possibly related to higher smoking in males. The tumor is slow growing, painless, and usually appears in the tail of the parotid gland near the angle of the mandible. In 5–14% of cases, Warthin's tumor is bilateral in 5 to 12 %l, but the two masses usually are at different times. Warthin's tumor is highly unlikely to become malignant.

Pathology
Warthins tumor is composed of glandular, often cystic structures, sometimes in form of papapilae. These are lined by a bilayered epitheliu, comprising of inner columnar eosinophilic or oncocytic cells

and outer smaller basal cells. The stroma contains dense lymphoid tissue that may harbor germinal centers and mantle zones. That is the reason for it to be named cystadenolymphoma, but this should not be confused with malignant lymphoma.It is well demarcated by a thin capsule. Very rare to have nuclear atypia or mitotic activity. Malignant change is rare (around1%) and may involve the epithelial or lymphoid component.

The differential diagnosis includes sebaceous lymphadenoma and oncocytoma.

Investigations

FNAC along with clinical profile is usually sufficient for diagnosis. Rarely CT or MRI is required, mainly when the diagnosis is not certain, deep parotid lobe tumor, associated facial nerve palsy or a fixed growth.

Treatment

Patients usually require superficial parotidectomy, which is curative. Recurrences are almost unknown.[15,16]

Mucoepidermoid carcinoma

In major salivary glands patient present with a solitary, rapidly growing mass. The history is usually short for around six months in around 50% of the patients two thirds are asymptomatic. The rest complain of pain, dysphagia, facial nerve palsy and trismus.

Epidemiology

In minor glands 40% are symptomatic, experiencing pain, dysphagia, hemorrhage and ulceration, etc. Mucoepidermoid carcinomas are seen throughout all adult age groups, but are most common in middle age (35-65 years of age) [7]. However, it is the most common malignant salivary gland tumour of childhood [7].

Overall, mucoepidermoid carcinomas account for:

- 2.8-15.5% of all salivary gland tumours
- 1-10% of all major salivary gland tumours
- 6.5-41% of minor salivary gland tumours

In the parotid gland they are the most common malignant primary neoplasm. A slight female predilection has been described, and radiation has been implicated as a risk factor.[17]

This tumor has a predilection for perineural spread, and careful and long term follow-up is therefore required and high grade varieties often present with early facial nerve involvement.

Pathology

This is the most common malignant salivary gland tumor comprising 35% of salivary gland malignancies. Around 50% are in major salivary glands. This tumor comprises of epidermoid cells, mucin producing cells and intermediate cells. It is multicystic with solid component. Cystic spaces are lined by mucous cells along with intermediate cells and few epidermoid cells. Keratinisation is rarely seen. The borders of the lesion appear well defined but infiltration of suurounding gland is invariably present.Mucoepidermoid carcinoma is classified as low, intermediate or high grade depending on the absence or presence of the following criteria:

1. Neural invasion given 2 points
2. Necrosis given 2 points
3. Anaplasia given 4 points
4. >4mitoses per high power field given 3 points
5. Less than 20%cystic spaces relative to solid areas given 2 points.

Based on these histological features, the tumor is graded as:

- Low grade if total score is 0-4 points,
- Intermediate grade if 5-6 points,
- High grade if 7+ points[17]

Investigations

Ultrasound

Typically a well circumscribed hypoechoeic, with an either part of completely cystic appearance. The lesion stands out against the relatively hyperechoeic normal parotid gland.

CT

Low grade tumours appear as well circumscribed masses, usually with cystic components. The solid components enhance, and calcification is sometimes seen. They have appearances similar to benign mixed tumours.

High grade tumours on the other hand, have poorly defined margins, infiltrate locally and appear solid.

MRI

Low grade tumours have similar appearances to benign mixed tumours :

- **T1** - low to intermediate signal ; low signal cystic spaces
- **T2** - intermediate to high signal ; cystic areas will be high signal
- **T1 C+ (Gd)** - heterogeneous enhancement of solid components

High grade tumours on the other hand have lower signal on T2 and poorly defined margins and infrequent cystic areas.

- **T1** - low to intermediate signal
- **T2** - intermediate to low signal

It is essential to image the cranial nerves with fat saturated post contrast T1 sequences to assess for perineural spread, and as such the base of skull should be imaged up to and including the cavernous sinus and inner ear.

Treatment and prognosis

Treatment is dependent on grade and location.

- Low grade (well circumscribed) can usually be treated with superficial or total parotidectomy and preservation of the facial nerve, without the need for neck dissection or adjuvant radiotherapy
- High grade (poorly circumscribed) usually requires radical parotidectomy, often with sacrifice of the facial nerve, neck dissection (as nodal metastases are common) and adjuvant radiotherapy

Prognosis is also very dependent on grade, with low grade tumours having a 90 - 98% survival and a low local recurrence rate, compared to 30 - 54% surviving, and a very high local recurrence rate for high grade tumours [17]

Adenoid cystic carcinoma also known as cylindroma[18]

This is the second commonest malignancy of the parotid gland and the commonest malignancy of the minor salivary glands. It forms around 22% of salivary gland tumors

It has a perineural spread and a hematogenous spread. Spread to the regional lymph nodes only in 20-25%of cases. It can have long periods of indolence with sudden spurts of growth. The commonest distant metastatic site is lung for adenoid cystic carcinoma. In some patients it might have an aggressive course. Recurrences are frequent and almost always late and difficult to predict.[18]

Pathology

Morphologically, three growth patterns have been described: cribriform, or classic pattern; tubular; and solid, or basaloid pattern. This pattern is similar to the cylindroma of skin and this is the reason its other older name. The tumors are categorized according to the predominant pattern.

***Grading*:**

- Low grade: tubular and cribriform pattern
- Intermediate grade: 30% to 70% solid pattern
- High grade**:** >70% solid pattern

Clinical features

It usually occurs in the 5^{th} to 6^{th} decade with a slight male preponderance. It is slow growing but may show aggressiveness. Five year survival rates are 60%, 10 year is 30% and 15 year recurrence rate

is 15%. Recurrences by the pathological variant are also predictable e.g. solid (100%), cribriform (89%), tubular (59%)

Investigations
All investigations are similar to other tumors. Confirmation is mainly after surgery.

Treatment
Because of chances of late recurrence, total parotidectomy with preservation of facial nerve if not involved and radical parotidectomy with facial nerve excision in patients with nerve involvement.[18]

Adenocarcinoma[19]
They have been classified as Acinic cell carcinoma, polymorphous low grade adenocarcinoma and adenocarcinoma not otherwise specified (NOS).

(a) Acinic cell carcinoma

Acinic cell carcinoma forms about 1-3% of all salivary gland tumors and 3% of all parotid salivary gland tumors. It is the second commonest childhood salivary gland malignancy after mucoepidermoid carcinoma. There is incidence of 10-15% metastasize (usually to local lymph nodes), 10-30% may have a recurrence (this is usually attributed to inadequate excision). The 5 year survival 90%, and 20 year survival is 60%.it has less aggressive behavior in in minor salivary glands.

Pathology
At scanning power, basophillia and prominent lymphoid infiltrate should raise suspicion of acinic cell carcinoma. The tumor shows multidirectional differentiation towards acinar, ductal as well as myoepithelial elements. Some tumor cells usually demonstrate differentiation towards acinar cells

Treatmen*t* - Excision

(b) Polymorphous low grade adenocarcinoma

Second most common palate tumor (after adenoid cystic carcinoma); it occurs in major salivary glands, usually associated with pleomorphic adenoma. Median age of presentation is 54 years (range 22-71 years) the incidence is more in women as compared to men. It is slow growing, but not painful. More than focal papillary growth is associated with cervical nodal metastases

Pathology
It is nonencapsulated but often well circumscribed tumor with diverse (polymorphous) growth patterns (cribriform, fascicular, microcystic, mixed, papillary [focal], pseudoadenoid cystic [without true lumens], single file, solid, strand-like, tubular)

Treatment - Excision[19]

(c) Adenocarcinoma NOS[19]

It is an Invasive tumor, often aggressive, with glandular or ductal differentiation but no features characteristic of other specific types. This is a commonest in all the variants of adenocarcinoma. It comprises of 5-10% of all salivary gland tumors and 17% of parotid gland malignancies and 15% of minor salivary gland malignancies.

Epidemiology

The Mean age 58 years (median 67 years), range 10-93 years. The gender predominance is debated, but recent reports show male predominance

Clinical features
The patient is usually asymptomatic other than the lump. It is often fixed to skin or deep tissues. The palatal lesions often ulcerated and involve the underlying bone. Patient present with cervical lymph node metastases in 23% of patients and distant metastases in 37% of patients. The 5 year disease specific survivals is 57%.

Pathology

The tumor shows invasive with glandular or ductal differentiation but no features characteristic of other specific type. The patterns include glandular spaces with cyst formation, papillary formation, solid sheets, comedonecrosis, hyalinized “shadow” nodules. There are also small clusters of cuboidal, round or ovoid cells with distinct borders and abundant cytoplasm. The tumor may be low, intermediate or high grade based on cytomorphic features. In situ component is seen in 68% of patients.

Treatment- Excision[19]

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Life After Transplantation

Sandeep Guleria

Human organ transplantation ranks as one of the most outstanding achievements in medical history. The procedure involves the expertise of various branches of medicine and is often the only hope for survival for patients. Advances in immunosuppressant technology are translating into not only longer graft survival, but also transplant of organs like bones, uterus and even intestines.

Life after transplantation is striking the right balance between rejection and infection .

Historical Aspects

The refinement in vascular anastomosis pioneered by Alexis Carrel, father of transplantation, led to attempts at solid organ transplantation in the early nineteenth century. Voronoy is credited with the first renal allograft (1933-1949). However, all they failed, as the concept of immunology was largely unknown. Gibson and Medawar carried out experiments on skin transplantation in response to search

for treatment of badly burned pilots in Second World War. They concluded that an auto graft survives indefinitely, while an allograft is not only destroyed, but induces memory and accelerated destruction in further transplants. Murray et al did the first successful renal transplant between identical twins in 1954. Starzl first attempted liver transplantation in man in 1963. The first successful clinical heart transplant was performed in 1967 by Dr. Christian Barnard at University of Cape Town. Hardy performed the first human lung transplant 1963 in a patient with carcinoma left lung. Kelly at the University of Minnesota initiated pancreatic transplantation in 1966.

However, the success rate was very limited until effective immunosuppresion was developed. Among the first drugs to be used was Azathioprine, developed by Ellion and Hitchings, used for renal transplants by Murray. Steroids were added to the immunosuppressive regimen later. Cyclosporine, discovered by Borel in 1976 was the most significant advance in immunosuppression. Calne is credited for introducing its widespread usage, initially in renal and later to all transplants.

The success rate further improved with the use of tarolimus and mycophenolate mofetil. Added to this were the new generation monoclonal antibodies like Rituximab, Eecluzimab, and Basiliximab

Types of Grafts

- Allograft: Transplantation from one individual to another
- Isograft: Transplantation between identical twins
- Xenograft: A transplant performed between different species
- Orthotopic: A transplant placed in its normal anatomical site
- Heterotopic: A transplant placed in a site different to that where the organ is normally located

The transplant operation is now well standarized and there are a number of patients with a liver or a kidney transplant whom the general surgeon od physician may get to see with a wide array of problems peculiar only to this group of patients.

Patient Survival

In developing countries dialysis facilities are inadequate and mostly in the private sector using machines that are poorly maintained and refurbished. Water quality is often poor with very high aluminium content resulting in high blood and bone aluminium level. Infections are a major cause of morbidity and the second main cause of mortality (after cardiac causes) in this group due to overcrowding, malnutrition and the use of temporary catheters. The annual patient mortality of patients on dialysis is reported as high as 80%.

Renal transplant is associated with a far superior patient survival. The only limitation being that the patient has to have a live related renal donor. Deceased donor transplantation has picked up but is still predominantly in the south. The one year patient survival is currently at more than 93% and the ten year graft survival at 58%. We are thus seeing a larger number of these patients with renal allografts in the general population.

Quality of Life

There are innunmerable studies that have clearly demonstrated that patients have an excellent quality of life post transplantation. Most go back to their original jobs are socially active and view the transplant as a second birth. Some patients have become parents after receiving a successful transplant

Rejection

1. ***Hyperacute Rejection*** (HAR) (Usually Occurs on the table)
   It is due to presensitisation of the recipient to an antigen expressed by the donor. The recipient has circulating antibodies prior to transplant owing to prior exposure through pregnancy, previous transplants or blood transfusion to donor alloantigens. A complement-mediated lysis is initiated resulting in immediate graft thrombosis. The graft swells up and becomes blue and hard on the operating table itself. The only measure against it is prevention. The tests used preoperatively are the ABO compatibility and lymphocytotoxicity cross match. They effectively prevent HAR in 99.5% of transplants.

2. ***Accelerated Rejection*** (Vascular Rejection)
   This is a delayed variant of HAR. The mechanism seems to be presence of alloantibodies at levels undetectable buy the crossmatch assay, in spite of presensitisation. Sometimes, massive

antibody production by T cell dependant B cell activation may cause de novo accelerated rejection. Thus, the graft initially functions well, but deteriorates by day three. Pulse therapy and plasmapheresis may reverse the condition in certain cases.

3. ***Acute Rejection*** (AR)
   This is a T cell dependant process and the only variant that can be effectively treated. It commonly occurs within the first six months of transplant. Acute rejection is invariable in transplants between non identical twins without immunosuppresion. The incidence of acute rejection declines with decreasing MHC disparity, though even a full house match mandates immunosuppresion. Activation of CD4 T cells leads to IL-2 secretion ultimately resulting in massive infiltration of the graft of mainly CD8 cells and its destruction. A cell-mediated counterpart of HAR is also known; presensitisation at T cell level causing accelerated form of acute rejection mediated by memory T cells. Prompt recognition and treatment leads to graft function retrieval in 90 to 95% of patients. Biopsy should be performed in unexplained graft dysfunction (Impaired LFT, raised liver enzymes, increased urinary amylase). Biopsy would reveal lymphocytic infiltration (eosinophilic also in liver). In renal transplant, the onset of oliguria, weight gain, hypertension and impaired renal function signals AR. The classic signs of fever, graft enlargement and tenderness are seen infrequently in patients treated with cyclosporine. The differential diagnoses could be calceneurin toxicity (Levels are high), Acute tubular necrosis, extrinsic compression on the graft or ureteric obstruction.

   Diagnostic modalities include renal diuretic scan with pertechnetate Tc 99, Ultrasound (prominence of renal pyramids and loss of renal sinus fat, hematoma) and MRI (loss of CMD). This can occur any time after the transplant and patients are advised to follow up regularly with their transplant units. Most acute rejections can be treated with a three day course of intravenous methyl prednisolone

4. ***Chronic Rejection*** (Chronic Allograft Nephropathy) (CR)
   This is a poorly understood process leading to insidious, slow and irreversible graft loss. It usually occurs over a period of months to years. It is not treatable by any method yet. Histologically it is characterized by replacement of graft parenchyma with fibrous tissue with a relatively sparse lymphocyte infiltrate. Non-immunological factors may also play a part. AR may sometimes cause rapid deterioration in a known case of CR and if treated, may lead to partial return of graft function. The only treatment is retransplantation.

Immunosuppressant Drugs

Immunosuppresion is a vital part of transplantation. However, it is a double-edged sword, carrying with it the risks of infection and malignancy, apart from the side effects of the drugs itself. The immunosuppression in the initial postoperative period is intense as the chances of rejection are maximum during this period, known as induction immunosuppression. They are also used as Rescue agents, used to reverse an established rejection episode. The dosage of immunosuppressants gradually tapers off, known as maintenance immunosuppression.

Since there is a large pool of these patients now adverse effects peculiar to this group of drugs are also seen. Most patients will be on triple drug immunosuppression comprising of tacrolimus, mycophenolate mofetil and steroids

The various drugs available for immunosuppression are:

1. ***Steroids***
   The most commonly used steroid is Prednisolone. It alone is ineffective and usually is added to Azathioprine and Cyclosporine in the most commonly used regimen for immunosuppression. The glucocorticoid effect causes a generalized immunosuppression by blunting T-cell proliferation. High dose Methylprednisolone (500-750mg/day IV bolus X 3-5 days) is used as a rescue agent for reversing acute rejection. Steroids are responsible for cushingoid features like acne, obesity, diabetes and peptic ulceration. They may cause growth retardation in pediatric transplants. The trend now is towards minimal steroid usage and even steroid free immunosuppression.
2. ***Mycophenolate Mofetil*** (MMF)
   It is also an antimetabolite. It is a reversible inhibitor of IMP dehydrogenase, interfering in Nucleic acid synthesis. It is relatively specific against lymphocytes as they lack the salvage pathway

(HGPRT catalyzed GMP production). Both T and B cell proliferation in response to antigen stimulation is blocked. The drug has potential for both induction and maintenance therapy. The side effects, including bone marrow depression are minimal. It is gradually replacing Azathioprine, especially in patients with high risk of rejection. It is regularly used in liver transplants in place of azathioprine due its low hepatotoxicity.

3. ***Tacrolimus*** (FK506)
   It is a macrolide calcinuerin inhibitor. It blocks IL-2 translation by binding to FK Binding Protein, the effect and toxicity being additive to cyclosporine. Tacrolimus is 100 times more potent than cyclosporine. The side effect profile is similar to cyclosporine, with more pronounced neurological and diabetogenic effect Tacrolimus is currently the drug of choice for renal and liver transplantation.

4. ***Azathioprine***
   The first immunosuppressive used, it is an antimetabolite. It is a prodrug, which is metabolized to 6-Mercaptopurine and then its derivatives. These then deprive the cell of adenosine, a vital ingredient in DNA synthesis. It is relatively nonspecific acting on all rapidly dividing cells. Its chief use is for maintenance immunosuppression and has no value as induction or rescue agent. It is rarely used in liver transplants. The dosage is usually 1-2 mg/kgBW. The dose limiting side effects are bone marrow depression and hepatotoxicity. Hence, the dose is withheld or reduced if TLC is less than 3000 cells/cc or liver dysfunction is present.

5. ***Cyclosporin***
   Discovered by Borel in 1976, it came into clinical practice in 1983. It is at present the mainstay of maintenance therapy in almost all type of transplants. It is a calcinueurin inhibitor, binding cyclophilin and inhibiting the transcription of IL-2 gene and thus T cell activation. It is remarkably specific against immunocompetent lymphocytes. However, it cannot be used as rescue agent presence of IL-2 in the graft bypasses the drug effect. At present, a micro emulsion formulation that has better bioavailability and pharmacodynamics is used. Since most of the metabolism is through the cytochrome P 450 enzyme system, Hepatic dysfunction mandates reduced dosage. The absorbed drug is almost totally metabolized and excreted in bile. Also, drugs influencing the cytochrome enzyme system alter the metabolism of cyclosporine (increased by rifampin, Phenobarbital, Phenytoin, decreased by ketoconazole, erythromycin and calcium channel blockers). The usual dosage is 7.5 to 25mg/kg. The main toxicity is Nephrotoxicity due to vasoconstrictor effect on proximal renal arterioles. Hyperkalemia, Hemolytic Uremic syndrome, Hypertrichosis, Gingival Hyperplasia, Neurotoxicity are the other side effects seen. This mandates strict monitoring of cyclosporine levels to avoid toxicity. Usually the level of cyclosporine 2 hours after intake is measured (C2levels).

6. ***Anti Lymphocyte Globulin/Anti Thymocyte Globulin*** (ALG/ATG)
   This is a polyclonal serum developed by collecting antibodies produced by various animals against human lymphocytes. Most commonly, Horse or rabbit are used. ATGAM is the purified IgG fraction most commonly used. The antibody coats the T cells and promotes its clearance. The drug is most commonly used as part of multidrug induction immunosuppression. Severe thrombocytopenia is occasionally seen. The patient is usually pretreated with antipyretics, antihistamines and antipyretics. Viral infections, both primary and reactivation are seen more frequently in patients treated with this drug.

7. ***Anti IL-2 Receptor Antibody*** (Basiliximab/ Daclizumab)
   The chimaeric monoclonal antibody basiliximab specifically binds the alpha subunit of the interleukin-2 (IL-2) receptor on activated T lymphocytes. Renal transplant patients usually receive basiliximab 20 mg 2 hours before and then 4 days after transplantation surgery. These antibodies have been shown to reduce the incidence of acute rejection without increasing the incidence of opportunistic infections or malignancy. Side effects are not very significant. Longer follow up however, is required to fully evaluate the efficacy of these agents.

Complications of Immunosuppression

Immunosuppression is not obtained without paying a significant price in terms of side effects. Infection and malignancy are the most frequent complications encountered with the use of non-specific immunosuppressive agent.

a) ***Infection***

Optimal use of immunosuppressive drugs in a renal transplant recipient (RTR) requires a careful balancing act. Availability of potent and specific immunosuppressive agents has reduced the incidence of acute rejection to about 10–15% in most centers. However, despite refinements in diagnostic techniques and discovery of new anti-microbial drugs, the risk of infection amongst transplant recipients has not come down. About 70% of all RTRs experience at least one infection episode by 3 years.. Infections are responsible for 18% of all deaths with functioning grafts in the US, and are the leading cause of death in the developing countries.

Infection risk is even greater in the pediatric transplant population. Infections also increase the risk of new onset diabetes after transplantation (NODAT), cardiovascular events, post-transplant lymphoproliferative disorders (PTLD) and adversely affect allograft outcomes.

Bacterial infections are approximately twice as frequent as viral infections in RTR. About 13% of all patients transplanted between 1996 and 2000 in the US required hospitalization for bacterial infections in the first 3 years compared to 6% for viral infections. Vascular access and urinary tract infections (UTIs) were the most frequent bacterial infections, whereas cytomegalovirus (CMV) was the commonest viral infection. Extremes of recipient age, female gender, deceased donor source, older donor age, CMV+ve donor, time on dialysis and systemic lupus erythematosus (SLE) as the cause of kidney disease increased the infection risk.

The infection risk at any given time after transplant is determined by the overall balance between the nature and intensity of epidemiologic exposure, net status of immunosuppression and the current nature of protection as determined by the vaccination and chemoprophylaxis status. Evaluation of exposure requires obtaining a history of travel to areas where certain infections may be endemic, dietary habits (e.g., cryptosporidium from well water and Salmonella and Lisetria from uncooked meat or dairy products), and details regarding work and hobbies (Aspergillus from construction sites, saprophytic fungi from gardening and leptospirosis in field workers). The overall status of immunosuppression is determined by complex and dynamic interactions between the recipient (age, gender, genetic background, underlying clinical condition), the transplanted organ and drugs. It is also affected by other complications such as a breach in the integrity of muco-cutaneous barriers, leukopenia, NODAT, poor graft function, liver dysfunction and malnutrition.
No consistent relationship has been shown between a specific immunosuppressive agent and overall infection risk. Mycophenolate mofetil (MMF) has been linked to an overall increase in infections, especially viral and antilymphocyte antibody to CMV reactivation. Higher incidence of BK virus nephropathy has been noted amongst those on the “potent” combination of tacrolimus and MMF.

The right level of immunosuppression that affords protection against rejection while minimizing infection risk is achieved in clinical practice by trial and error, based on monitoring of drug levels, leukocyte counts and surveillance for metabolic complications. Studies on evaluation of biomarkers for immune monitoring have focused toward identification of rejection. No reliable method exists currently for objective evaluation of net status of immune system to predict infection risk.

The possibility of infection needs to be considered in all febrile presentations of RTR. Fever may occasionally be absent, and symptoms may solely be related to one or more organ systems. The presentation may be different in RTR compared to the general population. For example, parvovirus B19 infection presents as pure red cell aplasia in this group, in contrast to erythema infectiosum in immunocompetent individuals. BK polyoma virus infection, asymptomatic in general population, causes renal allograft dysfunction.

The possibility of infections with unusual, often exotic, organisms and the high likelihood of polymicrobial infections necessitate a multidisciplinary approach with involvement of other specialists including the ID team. Early and aggressive use of imaging techniques such as ultrasound, computed tomography (CT) scans or magnetic resonance imaging (MRI), and invasive procedures like bronchoalveolar lavage, imaging guided aspiration and/or biopsies for obtaining specimens for histological and/or microbiological examination are essential for accurate diagnosis.

Serologic tests are of limited value since antibody response is attenuated in the immunocompromised host. Quantitative nucleic acid based assays are sensitive, quick, and useful for detection of subclinical infection, assessing response to therapy and identifying drug resistance. The non-specific nature of presentation often necessitates the initiation of broad-spectrum therapy before a specific etiologic diagnosis can be made. Development of CMV or EBV disease indicates over immunosuppression and should prompt reduction in immunosuppressive drug dosage.

Prevention of Post-transplant Infections

Adoption of preventive strategies has considerably reduced the burden of infection in RTR. This process starts before transplantation with pre-transplant screening of donors and recipients, avoidance of use of blood products, use of leukocyte filters during transfusions, treatment of pre-existing infections, immunoprophylaxis (vaccination), and continues after transplantation with tailored chemoprophylaxis and surveillance.

Donor screening is aimed at preventing transmission of latent infections including locally prevalent ones, e.g., tuberculosis and schistosomiasis, via the infected organ.Organs from with hepatitis (B or C) (HBV or HBC) or HIV infected donors are not used for transplant. Recently, some centers have started using organs from HCV or HIV positive donors for recipients who already harbor these infections after informed consent is obtained.

b) ***Malignancy***

As more people receive organ transplants, the incidence of post-transplant malignancy is increasing. These patients present an even more complicated picture than the usual cancer patient because they bring with them the added burden of immunosuppression and its unwanted consequences. The cancers that develop in transplant recipients are often more aggressive than those that develop in their non–transplant-associated counterparts and thus warrant rapid escalation in therapeutic intervention. Transplant recipients should undergo frequent, regular cancer screening. New advances in immunomodulation and novel agents should continue to improve outcomes for this select group of patients. Studies have reported the cancer incidence in the kidney transplant population to be as high as 40% in patients 20 years after transplant; this is compared with a 6% cumulative risk for cancer in an age-matched, nontransplanted control population . Malignancy is the reported cause of death in up to 26% of kidney transplant recipients who survive for at least 10 years The most common malignancies encountered in the post-transplant setting are nonmelanoma skin cancers (NMSCs) (up to 82% of transplant recipients), PTLD (1%–11%), and KS (6%) . Others, including non-Kaposi's sarcomas and gastrointestinal, urogenital, and thoracic tumors, have also been reported .

NMSC

Epidemiology

NMSC is the most common malignancy to develop after solid organ transplant, especially after kidney transplantation . Squamous cell cancer (SCC) is the most common subtype, with an incidence 65–250 times higher than that of the general population . The incidence of SCC increases with the length of post-transplant follow-up, thereby supporting the argument that the development of SCC is associated with cumulative exposure to immunosuppressive agents . SCC is an aggressive disease in transplant recipients . Half of those who develop NMSC are likely to develop a second NMSC within 3.5 years, with men having a significantly higher risk for recurrence than women . A poor prognosis is associated with the presence of multiple tumors, tumors on the head, extracutaneous tumors, older age, poor histologic differentiation, tumor thickness of >5 mm, and invasion of underlying tissue .

Greater sun exposure and fair skin type play an important role in skin cancers after transplant, because UV-induced *p53* tumor-suppressor gene mutations have been demonstrated in NMSC tissue from transplanted patients . As with most tumor types arising after solid organ transplantation, immunosuppression is often cited as the primary culprit because immunosuppressed patients are susceptible to infection with viruses such as EBV, herpes simplex, herpes zoster, and polyoma, all of which have been implicated in oncogenesis .

Transplant recipients should be warned as to the dangers of sun exposure. They should undergo full skin exams by their transplant care provider. Studies have demonstrated a benefit to systemic retinoid chemoprophylaxis

After development of skin cancer, patients should be treated aggressively because of the high risk for metastasis, recurrence, and death. Standard therapies include Mohs micrographic surgery, superficial ablative therapy, cryotherapy, and photodynamic therapy. As with most other transplant-related malignancies, attenuation of the immunosuppressive regimen is useful for controlling tumor progression.

PTLD

The term PTLD refers to a disease spectrum ranging from infectious mononucleosis to malignant lymphoma and resulting from uncontrolled lymphoid growth in an immunosuppressed transplant recipient . In adult solid organ recipients, PTLD has been reported in up to 2.3% of kidney transplants, 2.8% of liver transplants, 6.3% of heart transplants, 5.8% of heart–lung transplants, and 20% of small bowel transplants . PTLD is the most common post-transplant malignancy among pediatric transplant recipients . Indeed, transplantation at <18 years of age and male gender are independent risk factors for developing the disease

Immunosuppression is an important risk factor in the development of PTLD, though questions remain as to whether the specific immunosuppressive drug or immunosuppression, per se, is to blame.

The molecular pathogenesis of PTLD is most likely a result of the combined effects of immunosuppressive agents and infection by oncogenic viruses such as the EBV . In an uncompromised host, EBV-infected cells are killed by EBV-specific cytotoxic T lymphocytes (CTLs). In an immunosuppressed transplant recipient, however, EBV-infected cells may proliferate beyond the ability of CTLs to clear them . Subsequently, constant lymphocytic stimulation in the setting of a foreign allograft, either in the presence or absence of EBV, may be important in the development of mutations and eventual malignancy. In addition to EBV, the presence of genetic or epigenetic mutations can also lead to the development of PTLD: molecular alterations of *BCL-6*, c-*MYC*, and *p53*, DNA hypermethylation, and aberrant somatic hypermutation have been implicated in PTLD . EBV infection also appears to play a temporal role in PTLD outcomes. Early, polymorphic lymphomas are usually EBV positive and respond well to immunosuppression reduction . Late-onset, monomorphic disease is usually EBV negative, unresponsive to immunosuppression reduction, and associated with a worse prognosis. The pathophysiology for such late cases is unclear, but they may be a result of unidentified viral agents, loss of EBV, or incomplete diagnostic techniques . The increased division of lymphocytes caused by EBV infections yields an increased rate of new mutations. One of these mutations may lead to the replication of the cell independent of the presence of EBV. Over time, the EBV virus is lost, and the non-EBV–driven cells replicate in an unregulated manner.

Clinically, PTLD has variable presentations not clearly dependent on subtype. As with nontransplant-related lymphoma, the most common symptoms are nonspecific, including fever, lymphadenopathy, weight loss, abdominal pain, and splenomegaly . Rarely, patients present with multiorgan failure . PTLD usually presents at extranodal sites, with the gastrointestinal tract being the most common site aside from the allograft itself. As with most lymphomas, excisional biopsies should be obtained to allow for examination of architecture, and fine-needle biopsy should be avoided whenever possible. Immunohistologic staining for EBV is vital for diagnosis .

Because EBV has been implicated in the pathogenesis of PTLD, monitoring for the virus in serum has been considered as a means of prevention. The initial treatment for PTLD involves immunosuppression modification. Chemotherapy forms the backbone of therapy when the tumor progresses through immunosuppression reduction, and the most frequently used regimen has consisted of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).

Because of this high rate of treatment-related morbidity and mortality, the use of less-toxic agents such as rituximab, an anti-CD20 monoclonal antibody, has become more common.

Kaposi Sarcoma

Epidemiology

Prior to the AIDS epidemic and the increase in solid organ transplantation, KS was rare, comprising only 0.02%–0.06% of malignancies . However, the incidence of KS among solid organ transplant recipients is up to 500 times higher than that of the general population.

The pathogenesis of KS is most likely related to viral infection. The first association between an infectious agent and the development of KS was made when HHV-8, also called KS-associated herpesvirus, was isolated from KS tissue obtained from AIDS patients .

Surgical resection might be useful with isolated KS lesions [. However, immunosuppression reduction is the most common primary therapy, with consistent reports of CRs resulting from this intervention alone . However, loss of grafts secondary to chronic rejection was also reported, thereby highlighting the delicate balance between risk and benefit associated with immunosuppression reduction.

The replacement of immunosuppressive drugs has also shown some promise. As with PTLD, cyclosporine has been associated with a higher risk of developing KS . Switching to sirolimus might provide a useful alternative.

Other complications: are mostly due to the use of steroids : Cushing's syndrome, cataracts, gastrointestinal bleeding, hypertension, pancreatitis, and avascular necrosis of the femoral heads.

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Advances in Management of Urolithiasis

Madhu Sudan Agrawal, Manoj Sharma

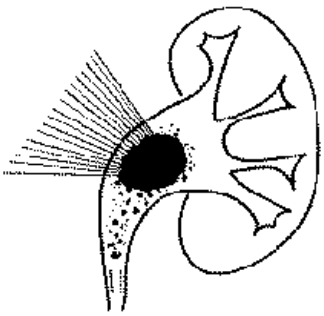
Urinary stone disease is one of the oldest diseases known to mankind, the reference of which is found in the oldest medical texts available. In absence of effective medical therapy, for many years surgery was the only definitive treatment for the relief of symptoms. However in the recent years dramatic advances have been made in the management of urinary stone disease, and a number of nonsurgical and virtually atraumatic approaches have come into vogue for stone removal.

Before the newer minimally invasive technologies became popular, conventional stone surgery was the only option, but as far as the patient undergoing operation is concerned, it carried definite hazards. Postoperative pain at the operation site, wound infection, hernia formation and prolonged urinary drainage were but a few of the not uncommon complications. In addition, the significant period of hospitalization and prolonged recovery phase required after open operation and the resultant loss of earnings and work days also are significant. Yet another factor is the frequent need for second and sometimes multiple operations due to recurrent nature of stone formation.

It is in the promise of avoiding these problems that the primary attraction of the new minimally invasive technologies lies. The first of these is Extra-corporeal shock wave lithotripsy, or just LITHOTRIPSY, a technique which involves “in-situ disintegration of stones” and offers for the first time a simple, safe and effective method of getting rid of the urinary stones without conventional open operation.

Extracorporeal Lithotripsy (E.S.W.L.)

The most innovative medical discovery of recent times, extra corporeal lithotripsy makes use of high frequency shock waves focused on the stone from outside the body (hence ‘extra-corporeal’) for disintegration of the stone. Developed in Germany in early 1980’s, the equipment consists of a shock-wave generator, a focusing mechanism, and a monitoring device.[1] (Fig 1)



The shock-waves are generated by high-voltage spark or by peizo-electric effect, and are focused on the stone with a semi-ellipsoid reflector. These shocks pass through body tissue (including renal parenchyma) without any damage due to its high fluid content, and act only on the brittle textured stone by progressively disintegrating it.Bi-planar fluoroscopy is used for stone localization and accurate patient positioning. The stone is impounded by bursts of shock waves (2500-3000 shocks in one sitting, each shock wave of 0.5–1.0 microsecond duration) and the disintegration of stone is monitored on fluoroscope. Complete disintegration of an average sized stone takes 30–45 minutes, and the fragments left behind are gradually cleared off in urine over a period of several days to weeks. Some larger and harder stones may take more than one sitting for complete fragmentation.

Despite its relatively high cost, ESWL became immensely popular largely due to its near complete non-invasiveness. The technique is now available in more and more centres across the country. With new and more advanced machines the procedure can be done without anaesthesia (or under sedo-analgesia) on a completely outpatient basis without hospitalization. The initial high cost of treatment is more than offset by early return to work and livelihood. The procedure is best indicated for small, medium sized stones (up to 2 cm) in non-obstructed normally functioning kidneys.

Early reports enthusiastically promoted this new technology and SWL found application in even complex cases such as multiple stones, bilateral stones, stones in solitary kidneys and staghorn calculi.However, as experience with lithotripsy grew, urologists began to recognize its limitations. Some stone types (for example, brushite, calcium oxalate monohydrate, and cystine stones) could be resistant to SWL. In addition, fragmentation was not always complete, and the presence of residual fragments often necessitated re-treatment. Also, aspects of renal anatomy (lower pole calyx, acute infundibulo-pelvic angle, calyceal diverticula) could pose a barrier to the clearance of stone debris. In

addition, the relatively limited capacity of the ureter to discharge stone fragments restricted SWL treatment to a stone size of less than 2.0 cm.

Reports also began to describe unexpected and sometimes serious adverse effects of SWL. It became apparent that shock waves could rupture blood vessels and that the resultant bleeding could be severe. Case studies reported the occurrence of intra-parenchymal haemorrhage and massive renal hematomas requiring transfusion, or even nephrectomy. Extra renal damage such as intra-abdominal bleeding, splenic rupture and hematomas of the liver and pancreas were also reported.

Thus, against the background of countless successful cases were problems too significant to ignore. Studies conducted primarily in the pig model using the Dornier HM3 lithotripter (Dornier, Germany) found that the lesion was focal but not limited to the dimensions of the focal zone, that lesion size was dose-dependent (both number and amplitude of shock waves), and that the renal papilla was particularly susceptible to shock wave damage. These observations have led to the development of treatment strategies that can significantly reduce tissue damage in SWL.[2]

Obese patients typically have poor outcomes with lithotripsy, and treatment often fails in cases in which the skin-to-stone distance is greater than 9–10 cm. When the skin-to-stone distance is large, the stone cannot be positioned precisely at the focal point of the lithotripter without inverting the cushion of the treatment head—a situation almost certain to produce very poor coupling.

Contraindications to ESWL include (1) Some very hard calculi (eg. cystine, calcium oxalate monohydrate), (2) outflow obstruction, (3) Non-functioning kidney, (4) Large (> 2 cm) and staghorn calculi, (5) uncontrolled infection, hypertension, or bleeding diathesis, (6) pregnancy.

Percutaneous Nephro-lithotripsy (PCNL)

Endourological Lithotripsy, using ultrasound or electrohydraulic energy for breaking of stone, by definition is 'closed controlled manipulation of upper urinary tract' and treatment of upper urinary tract calculi is a major application of this relatively new science, which was developed in the late 70's in Scandinavia.[3] (Fig 2)

This approach is used for renal and upper ureteric calculi. In this approach, a needle puncture is made into the stone-bearing renal collecting system through the lumbar route, the patient lying in prone position. A guide wire is passed through the needle into the collecting system of kidney and the tract thus formed is dilated gradually to 34F size using serial coaxial Teflon or metal dilators. A nephroscope is passed through this tract into the collecting system of kidney and the stone is visualized.

The entire procedure is done using a C-arm Image Intensifier. Then under combined effect of endoscope and this C-arm Image Intensifier, smaller stones (upto 1.5 cm) are removed intact with grasping forceps, while the larger stones are broken up using ultrasonic, pneumatic or electrohydraulic lithotripter. The ultrasonic lithotripter consists of an ultrasound generator and a hollow ultrasonic probe, which transmits the ultrasound waves to the stone by direct contact. As the fragmentation proceeds, the smaller fragments are sucked out through the central irrigation channel of the probe, while the larger fragments are removed with especially designed grasping forceps.

Contraindications: The only absolute contra indications to PCNL include pregnancy and uncontrolled bleeding diathesis. By and large, the procedure is possible in majority of the patients, including those considered unsuitable for the other modalities like open surgery and shock wave lithotripsy.

Complications: Complications of PCNL include, injury to kidney and adjoining structures (liver, spleen, colon, etc), pleural injury, bleeding, pyrexia, extravasation, retained fragments, ureteric obstruction (clots, stone fragments etc in the early period, and stricture of PUJ, late presentation). Long term complication include (UPJ obstruction and AV fistula formation, though they occur in a very small percentage of cases.

New developments

Newer developments include those in imaging, technique and instrumentation. Traditionally, puncture for access was made under fluoroscopic guidance, while now **Ultrasound-guided** puncture is being used by more and more centers across the world to improve accuracy and reduce radiation exposure.[4] Whereas originally all patients of PCNL required a nephrostomy tube drainage post-operatively, in recent years **'Tubeless PCNL'** has found increasing favor with less post-operative pain and faster recovery.[5]

Advances in pre-operative imaging

Traditionally, conventional IVU has been the mainstay for imaging before PCNL, but recently a few studies reported the advantages of using CT as an imaging method before PCNL. Information such as the anatomy of the pelvi-caliceal system and relation of the stone to the pelvi-caliceal system, and insights into the three-dimensional anatomy of the renal unit, can be obtained with CT. A few studies showed the advantages of CT angiography for managing and treating bleeding after PCNL.Authors of a recent study suggested that patients at risk of colonic injury during PCNL should be assessed using prone CT before the procedure, as this helps in planning access sites and avoiding injury during access.

Another development is **Cone-beam CT (CBCT),** which helps to assess the preoperative plan of a percutaneous procedure and simultaneously to assess the postoperative clearance. CBCT uses an imaging head similar to that of a conventional C-arm to provide high-resolution, three-dimensional, CT-like images. CBCT might provide the advantages of improved preoperative imaging, which could result in better percutaneous access and improved postoperative imaging, which allows surgeons to have 'real-time' access to CT-quality images.

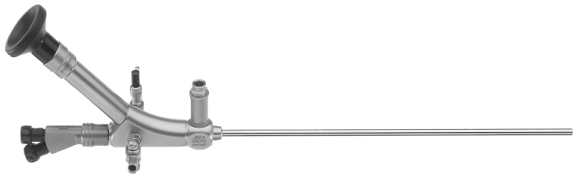
Advances in instrumentation

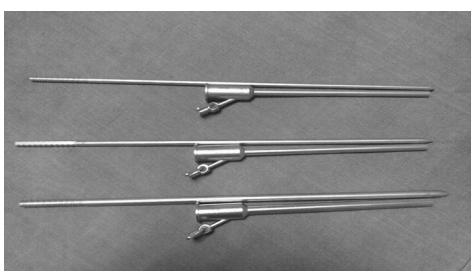
The **Stonebreaker** (Cook, USA), is a hand-held pneumatic lithotripter. The device is powered by a self-contained compressed carbon-dioxide cartridge. The device is also activated by a hand switch rather than a foot switch, which further eliminates trailing cords in the operating theatre. The Stonebreaker delivers 3.1 MPa to the stone via the treatment probe, compared with 0.3 MPa from pneumatic lithotripters. In a study comparing the Stonebreaker with the Swiss Lithoclast, the authors found that the Stonebreaker is easier to set up and is user-friendly, and provides faster stone fragmentation than the Swiss Lithoclast.

Cyberwand, a new tool by Gyrus ACMI (Olympus, Japan) is a dual ultrasonic lithotripter. As the two probes vibrate at different rates it produces a synergistic effect. The inner probe vibrates at a frequency of 21,000 Hz while the outer probe vibrates at 1000 Hz. The inner probe protrudes beyond the outer probe, and both are controlled with a single foot pedal. There are few reports describing the clinical outcome of this device.

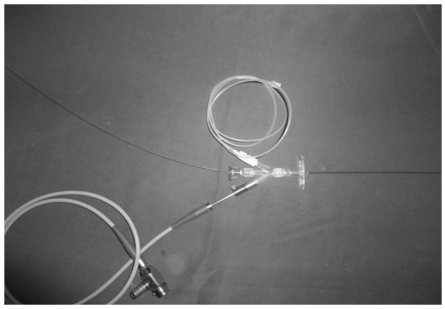
Mini-PCNL & Micro-perc

A major aim of development and innovation is to reduce the tract size, as this decreases the morbidity, as confirmed by several studies. The **Mini-perc** can be defined as a percutaneous procedure with a tract size of <18 F.[6,7] Currently mini-perc is performed with a nephroscope sheath of 14–16 F, with a nephroscope 12 F in size, using holmium laser as the fragmentation device. (Fig 3 & Fig 4)



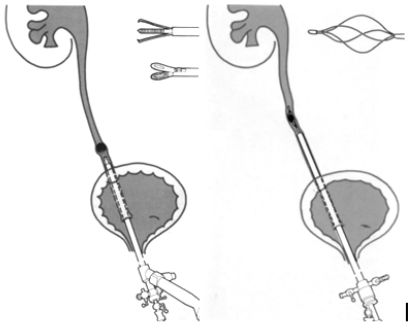


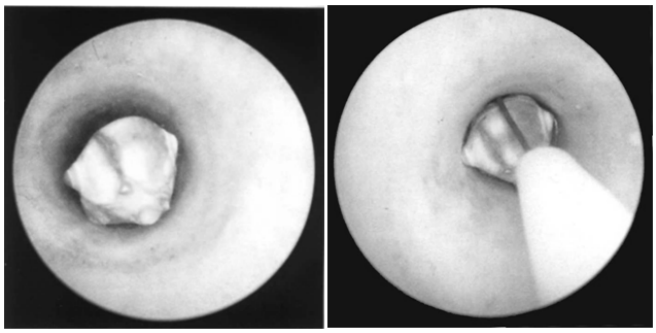
Desai and Bader[8] reported their experience with **Micro-perc** using a micro-optical system inserted through an 'all-seeing needle' of 1.6 mm (4.85 F) outer diameter to confirm the location of the chosen access and completion of stone fragmentation using this needle itself as the operating tract. Micro-optics of 0.9 mm in diameter were used along with 200 micron laser fiber. (Fig 5)



Ureterorenoscopy (URS)

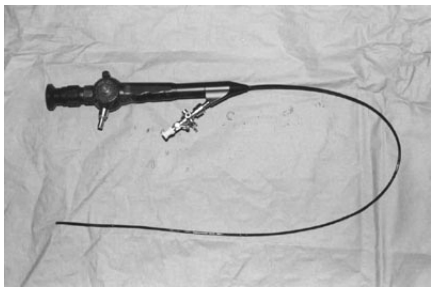
The first ureteroscopy is credited to Hugh Hampton Young, the 'Father of Modern Urology', who introduced a 12 Fr pediatric cystoscope into the massively dilated ureter of a child with posterior urethral valve in 1912. He was the first Urologist to view the intra-renal collecting system of a patient endoscopically. Urinary stones can be approached retrograde using the specially designed slim-body ureterorenoscope, which allows direct access to, and direct visualization of the entire length of ureter upto the renal pelvis. Stone removal is done in the same ways as PCNL by direct manipulation or pneumatic or laser lithotripsy.[9] (Fig 6 & 7)





Although it is a more invasive technique than SWL, ureteroscopy is the most efficient technique for treatment and removal of ureteral stones. When the ureteral orifice is too narrow to accommodate the ureteroscope, dilation may be accomplished with serial dilators, balloons, or even the ureteroscope itself. Complete fragmentation to a size less than that of the safety wire (0.035 inch) should allow passage of all fragments without difficulty. Alternatively, fragmentation to a size sufficient for extraction by a stone retrieval device achieves a stone-free statefor the patient at the end of the procedure. If significant ureteral edema or manipulation occurs, a double-J stent should be placed to prevent colic and obstruction.

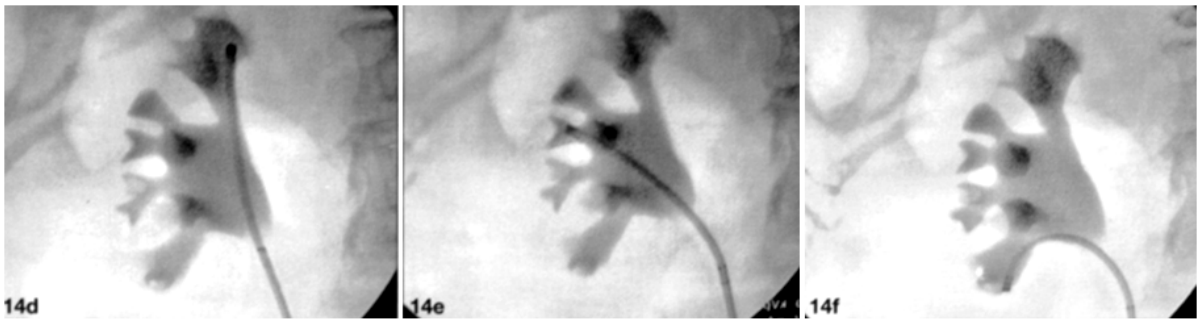
Technological progress has evolved flexible ureteroscopy or **Retrograde intra-renal surgery (RIRS)** into a safe and efficacious modality for the treatment of the upper urinary tract and has expanded its potential indications to intra-renal large stones (>25 mm), shock wave lithotripsy (SWL) failure, infundibular stenosis, morbid obesity, reno-ureteral malformations, musculoskeletal deformities, and bleeding diathesis. The development of flexible ureteroscopes and accessory instrumentation like guidewires, ureteral access sheaths, intra-corporeal lithotripters, and stone retrieval baskets has facilitated RIRS and has given more safety to the procedure. RIRS has progressed to be a real alternative to shock wave lithotripsy and percutaneous nephrolithotomy (PCNL) for treatingsmall- to moderate-sized renal calculi—offering the low morbidity of SWL combined with stone-free rates comparable with PCNL.[10] (Fig 8 & 9)



Summary

The indications for a mini-perc, retrograde intra-renal surgery (RIRS) and ESWL overlap. Both RIRS and the mini-perc are invasive and are associated with inherent complications. Similarly, opinions on the utility of the mini-perc compared with standard PCNL are divided. A retrospective study failed to

show significant advantages of the Mini-perc technique, but two randomized controlled trials comparing Mini-perc with RIRS and the other comparing Mini-perc with standard PCNL showed that the Mini-perc has a role. Both RIRS and the Mini-perc were effective in rendering patients stone-free with minimal complications. The immediate stone-free rate was higher with the Mini-perc but comparable in both methods at 1 month.



In addition to the extra benefit of short hospitalization, saving of workdays, and early return to work, one major advantage of endourological lithotripsy is complete removal of stone in one hospitalization in majority of cases, without any risk of residual stone or fragments. Endourology is most useful in the patients where Lithotripsy (ESWL) is contraindicated, including large (>2 cm), staghorn, or impacted stone, & dilated and obstructed collecting system, or poorly functioning kidneys.

The greatest limitation of endourological procedure is the great degree of technical complexity involved in its execution, which precludes its use by anyone than an expert endourologist. In the hands of the inexperienced it can be an extremely hazardous undertaking. The possible complications include perforation of the renal pelvis or ureter, damage to adjacent structures (including peritoneum, pleura, spleen, liver, duodenum, and colon), peri-operative hemorrhage, infection and septicemia.

Conclusion

Using singly or in combination, PCNL, URS and ESWL can take care of up to 99% of urinary tract stones**.** In very large and staghorn stones a combination of PCNL and ESWL can be used to achieve complete clearance of the stone. The near simultaneous advent of these procedures has revolutionized the management of urinary stone disease to the extent that already in many centers the world over, open surgery is being performed for less than 1% of stones. Encouraged by the tremendous success and acceptability of these lithotripsy techniques, surgeons and urologists are not mistaken in the belief that in years to come open surgery for stone disease will become a true rarity.

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Investigations in a case of Obstructive Jaundice

Rajdeep Singh

Investigations should have the following aims:

- Detection of disease (i.e. diagnosis)
- Assessment of severity
- Assess prognosis
- Assess effect of therapy / recurrence / follow up

When a patient reports with jaundice, the surgeon is faced with the following questions:

a) Is it obstructive jaundice?
b) What is the level of jaundice?
c) What is the extent of disease?
d) What intervention is indicated?

Investigations are directed to answer the above questions. The individual tests will be discussed first, followed by approach to a patient of jaundice (with emphasis on obstructive jaundice). Associated investigations are also indicated, though they would not be discussed here e.g. fasting blood sugar and ECG.

Liver Function tests

The term 'Liver Function Tests' includes bilirubin, aspartate transaminase (AST or SGOT), alanine transaminase (ALT or SGPT) and alkaline phosphatase (ALP). Some labs may include protein levels and gamma glutamyl transferase estimation (GGT) also.

Bilirubin

Elevated bilirubin is the hallmark of obstructive jaundice. Yellow discolouration of skin without jaundice may be seen in carotenemia. Invariably, bilirubin is tested simultaneously for direct bilirubin (conjugated bilirubin) and indirect bilirubin (unconjugated bilirubin) at the same time. Classically the van den Bergh test was done to assess the direct reacting fraction, and the indirect fraction is calculated after subtracting from total bilirubin. Nowadays, many laboratories would measure both fractions separately by spectrophotometry.

Conjugated hyperbilirubinemia is the hallmark of obstructive jaundice. However, it should be remembered that other conditions like viral hepatitis, and Dubin-Johnson's syndrome also cause rise of conjugated fraction. Hence, its value is primarily in differentiating haemolytic causes from other hepatic and post hepatic causes of jaundice.

The presence of bilirubin on urinalysis is also a marker for conjugated hyperbilirubinemia, since only conjugated bilirubin can be excreted by the kidneys. This is the basis for a very simple bedside observation- if the urine of a jaundiced patient is high coloured, it is likely due to conjugated bilirubin, a marker for hepatic and post hepatic causes.

Bilirubin may interact chemically with test reagents. It causes spuriously low results of creatinine, glucose, cholesterol, triglyceride, uric acid and phosphorus.[1]

AST and ALT

Aspartate aminotransferase (AST, SGOT) is an intracellular enzyme responsible for amino acid metabolism. It has 2 isozymes – Type 1 is cytosolic and found in a variety of tissues, and Type 2 found in mitochondria, and more specific to liver. Isozyme testing is hardly ever done in clinical practice. AST is present in liver, cardiac muscle, skeletal muscle, RBCs, kidneys and brain. Hence it is less specific than ALT.

Alanine transaminase (ALT, SGPT) is also an intracellular enzyme, responsible for amino acid metabolism. It is primarily present in liver cells.

Elevation of AST and / or ALT is a marker of cellular damage. Isolated rise of AST indicates non-hepatic cause for jaundice, such as muscle injury or myocardial infarction. The ratio of AST/ALT is

used as an indicator for alcoholic liver disease (this is partly due to relative reduction of ALT because of reduced pyridoxine); the ratio is 2:1 in such cases. Wilson's disease results in a ratio of 4:1. However, in most clinical situations which the surgeon will encounter, the levels of AST and ALT rise concurrently, giving a ratio of about 1:1.

AST and ALT rise whenever there is liver cellular injury, liberating intracellular enzymes. Thus it is elevated in viral hepatitis, liver trauma and in liver ischaemia (e.g. if the right hepatic artery is clipped during lap cholecystectomy!). Mild elevation is seen in obstructive jaundice too. High levels in a patient of obstructive jaundice should alert the surgeon to the possibility of cholangitis.

The commonest causes for an AST being greater than 10 times the upper limit of normal in a general hospital are hepatic hypoxia and calculus bile duct obstruction.[2]

Glutathione-S-transferase a-isoenzyme (GST-a) is a potential alternative to the transaminases for assessing hepatocellular damage. This enzyme has a short half-life of 90 min and may therefore be a sensitive and rapidly responding marker of liver injury.[3]

Alkaline phosphatase (ALP)
ALP is a canalicular enzyme, normally expressed by the apical part of hepatocytes. It is cleaved and secreted in the space of Disse, and thence in the bile. Obstruction to bile flow results in ALP 'overflowing' into the vascular system as well as increased synthesis by the hepatocytes. ALP is also produced by osteoblasts, kidney and salivary glands, among other tissues. Hence it is raised in bone metastases also. Although there are 5 isozymes which can be used to differentiate the source of elevated ALP, they are not available for clinical use. Therefore, most clinicians use GGT (gamma glutamyl transferase) or 5'-nucleotidase estimation to confirm that elevated ALP is due to obstructive jaundice. GGT is also used as a marker for alcohol use, since it is elevated in patients with alcohol abuse, even if there is no hepatic disease such as cirrhosis. If hepatic disease is present, other enzymes rise in parallel with rise in GGT.[4]

Serum Albumin
Marker for chronic liver disease, since most of the albumin is synthesized in the liver only. It should be remembered that the half-life of serum albumin is 21 days; hence a reduced albumin level indicates malnutrition that is more than 3 weeks old. Pre-albumin estimation has a shorter half life (7 days) hence lower levels indicate more recent loss of synthetic liver function.

Prothrombin Timed Ratio (PTI)
Synthesis of Factors I, II, V, VII and X occurs in the liver; therefore in liver disease these factors are not synthesized. Further, factors II, VII, IX and X are dependent on Vitamin K availability. Overall PTI measures the extrinsic pathway of coagulation. Since Vit K is fat soluble, it cannot be absorbed from the intestine in the absence of bile. Therefore, estimation of the PTI (or better the International Normalized Ratio, INR) is an indicator of liver function. A prolonged PTI in obstructive jaundice is due to inadequate Vit K; if the PTI does not come to normal even after parenteral supplementation, there is likely liver cell damage.

Hemoglobin
Estimation of hemoglobin is not directly contributory to the diagnosis of obstructive jaundice. It is mentioned here because the conventional Sahli's method of hemoglobin estimation will give a false high value, because the serum is already coloured yellow. Modern day automated analysers compensate for this error and usually give correct results. Cyanmethemoglobin test is the reference standard for hemoglobin estimation.

Tumour markers
Tumour markers are ordered in cases of hepatocellular cancer, gall bladder cancer or pancreatic cancer. Apart from alpha fetoprotein (AFP) levels in hepatocellular cancer, none are diagnostic. Their utility lies mainly in monitoring response to follow up. CA 19-9 [5] and CA 125 [6] have both been found elevated in Ca gall bladder.

Imaging

Ultrasound

Is the first imaging modality of choice in case of jaundice. The presence of gall bladder stones indicates a high possibility of choledocholithiasis, even though ultrasound is not a good modality for detecting CBD stones. It can also tell about the diameter of the CBD, the presence of intrahepatic biliary dilation, GB masses, liver masses, hydatid cysts, liver metastases, etc. It is not very accurate for pancreatic lesions. The major intra- hepatic bile ducts are normally 2mm in diameter, the common hepatic duct < 4 mm and the common bile duct <5–7mm in diameter.[7]

CT scan

Indicated for malignant lesions of the gall bladder, liver or pancreas. It is not a good modality for gall stones, with ultrasound being even more accurate than CT.[8] In general, CT is good for Liver and nodes, whereas MRCP is good for the biliary tree.

MRCP / MRI

The modality of choice for defining structural abnormalities in jaundice is magnetic resonance cholangio-pancreatography. It is very accurate for CBD calculi, and also for mural disease of the CBD, such as strictures, sclerosing cholangitis and choledochal cysts. Gadolinium contrast is used, which may result in nephrogenic fibrosis later on in life. Another drawback is that in the presence of gross ascites image quality becomes poor.

EUS

Endoscopic Ultrasound (EUS) is done using an endoscope which has a miniature ultrasound transducer mounted on its tip. It is at least as sensitive as ERCP in detecting stones and strictures.[9] The sensitivity and accuracy of endoscopic ultrasound for choledocholithiasis is greater than 90%[10] and it is more accurate than transabdominal ultrasound.[11]

ERCP

Endoscopic retrograde cholangio-pancreatography should not be used as a diagnostic modality. There is a definite morbidity of ERCP, and mortality has been reported. It is usually combined with a therapeutic procedure, such as stent placement or stone extraction. Diagnostic and interventional procedures such as biopsy or stone extraction is useful distal to the union of right and left hepatic ducts. Proximal to that PTC is helpful. ERCP may be unsuccessful in some patients due to anatomical factors, such as a perivaterian diverticulum or if the gastric anatomy is altered as after gastric bypass.

Table 1: Comparison of different imaging modalities:

Test	Sensitivity	Specificity	Comments
Ultrasound	55-91%	82-95%	Advantages: noninvasive, portable, least expensive Disadvantages: bowel gas may obscure common bile duct; difficult in obese individuals
CT scan	63-96%	93-100%	Advantages: noninvasive; higher resolution than ultrasound; not operator dependent Disadvantages: intravenous contrast medium required (potential nephrotoxicity)
MRCP	82-100%	92-98%	Advantages: noninvasive Disadvantages: requires breath holding; may miss small-caliber bile duct disease
ERCP	89-98%	89-100%	Advantages: provides direct imaging of bile ducts; permits direct visualization of periampullary region and acquisition of tissue distal to bifurcation of hepatic ducts; potential for simultaneous therapeutic intervention; especially useful for lesions distal to bifurcation of hepatic ducts Disadvantages: cannot be performed if altered anatomy precludes endoscopic access to ampulla (e.g., Roux loop). Morbidity 3% & mortality 0.2%
PTC	98-100%	89-100%	Advantages: provides direct imaging of bile ducts; potential for simultaneous therapeutic intervention; especially useful for lesions proximal to common hepatic duct Disadvantages: more difficult with non-dilated intrahepatic bile ducts. Morbidity 3% & mortality 0.2%

(from: Sleisenger & Fordtran's Gastrointestinal and Liver disease, 7th edition)

NBD-gram

Nowadays ERCP with stenting is the default intervention for a biliary obstruction. The older practice of

placing a long Naso-biliary drain (NBD) for external drainage, however, has advantages in that (a) we can get a sample for culture, especially in purulent cholangitis (b) injection of a radio-opaque dye can delineate the CBD very well, without the need for repeated ERCPs.

PTC / PTBD

Percutaneous transhepatic cholangiography (PTC) is indicated to image the proximal biliary tree. At one time PTC was mandatory to define proximal extent of a biliary stricture, the distal end defined by ERCP. This cumbersome procedure has now been replaced by MRCP, and PTC alone is rarely indicated nowadays. If performed, it is combined with a drainage catheter, in which case it is known as a percutaneous transhepatic biliary drainage (PTBD). PTBD is indicated for the relief of cholangitis with a tight biliary stricture. Occasionally it may be a temporary method to relieve jaundice, prior to a more definite procedure.

HIDA scan

Nuclear scintigraphy has no role in the evaluation of jaundice, since it is not taken up by the liver once bilirubin levels exceed 7-9mg%. Its role is limited to diagnosis of acute cholecystitis and for follow up after bilio-enteric anastomosis to confirm patency of anastomosis.

Approach to a patient with jaundice

The first step is to determine if the jaundice is medical or surgical (obstructive or not). The commonest disease is viral hepatitis, in which there is a prodrome of malaise, anorexia and aversion to cigarettes before clinical jaundice develops. The history is prone to errors however, and should be taken as indicative only. The sensitivities of history, physical examination, and blood tests alone range from 70% to 95%,[12] whereas the specificities are approximately 75%.[13]

Table 2: Obstructive jaundice vs viral hepatitis

	Obstructive jaundice	**Viral hepatitis**
History	RUQ pain Fever, rigors Prior biliary surgery Older age	Anorexia, malaise, myalgias Known infectious exposure Receipt of blood products/ iv medications Jaundice in family or locality
Examination	Abdominal tenderness Fever Abdominal mass Scar of previous surgery	Ascites Stigmata of liver disease
Investigations	Elevated ALP PTI normalizes with Vit K Positive imaging	Elevated AST/ALT PTI does normalize with Vit K Positive serological tests

(from: Sleisenger & Fordtran's Gastrointestinal and Liver disease, 7th edition)

The clinical impression is confirmed with investigations, the most important being LFT. Once a provisional diagnosis of obstructive jaundice is made, investigations are directed towards the cause for obstruction. Ultrasound is a good modality, which will give a provisional diagnosis in most of the cases, and directs what future investigations should be done. MRCP is the most common next step. Tumour markers are required only if imaging suggests a malignancy.

Child Pugh Score

The most widely used and best-validated prognostic index remains the Child-Pugh classification, which correlates with individual survival and also been shown to predict operative risk. This is applicable for all interventions; e.g. even a ventral hernia repair. Elective surgery should not be done in grade B or C.

Variable	**1**	**2**	**3**
Encephalopathy	Nil	Slight to moderate	Moderate to severe
Ascites	Nil	Slight	Moderate to severe
Bilirubin, mg/dl	< 2	2-3	>3
Albumin, g/dl	> 3.5	2.8 - 3.5	< 2.8
Prothrombin index	> 70%	40% - 70%	< 40%
Modified Child's risk grade (depending on total score): 5 or 6 points, grade A; 7 to 9 points, grade			

B; 10 to 15 points, grade C.

The MELD (Model for End stage Liver Disease) score is also now being used as a prognostic index, although it was developed for triaging patients for liver transplantation.

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