Current Studies in General Surgery

Editor

Yasin Kara

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PREFACE

Dear Colleagues,

We are pleased to have published the book, “Current Studies in General Surgery”, which consists of 8 chapters in the subjects of Totallly extrapreperitoneal hernia repairs, Abdominal wall hernias, Mastitis, Growth factors in the treatment of diabetic foot ulcers, Management of appendiceal neuroendocrine neoplasms, Diverticular disease of colon, Surgery in Tuberculosis and Ultrasound guided peripheral nerve block applications in chronic pain management. We believe that all the chapters will be read with great interest and are expected to contribute to the literature and serve as a reference for future studies.

The last 30 years has witnessed an unimaginable developments in scientific information available to practitioners of surgery. The “science of surgery” has gained dominance over the “art of surgery.” Diverse technologies have been incorporated to expedite diagnosis and improve surgical excision or repair. The establishment of more precise criteria for categorization and analyzing data, coupled with advances in informatics, has allowed for the practice of “evidence-based medicine and surgery.”

It is a singular privilage to serve as editör in chief of this “ Current Studies in General Surgery” Book.

I would like to thank to coordinators, referees, authors, readers and publisher for their devoted work.

Respectfully yours

Ass. Prof. Dr. Yasin Kara
Health Sciences University Kanuni Sultan
Süleyman Training and Research Hospital
Department of General Surgery
Editor

CONTENTS

CHAPTER I

TOTALY EXTRAPREPERİTONEAL HERNİA REPAİRS

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1. Introduction:

As the first laparoscopic cholecystectomy was successfully performed in 1985 by Muhe et al. Laparoscopy as minimally invasive technique is replaced many open procedures used in treatment of many diseases in general surgery practice. (1) Totally extraperitoneal repair (TEPR) has some well known and proven advantages as less pain, early ambulation, early return to routine life and work, good cosmesis and less wound infection. In the past, Inguinal hernias were treated with methods of open repair (for example, the Bassini method), which repair the hernia defect by suturing inguinal floor. Nowadays, the production of prosthetic prolen meshes has led to an increase in the number of 'tension-free' methods of reinforcing the inguinal floor region. Open techniques using mesh are classified as traditional tension free mesh (as the Lichtenstein technique), open placement of preperitoneal mesh (the Nyhus and Stoppa techniues) and open placement of mesh plug repair (The Rutkow technique). These open methods of hernia repair are associated with more postoperative pain, wound infection and scrotal sensation problems due to the open inguinal incision.

In their current prospective randomized controlled study, Prakash et al. reported the rate of chronic pain following the TEPR as 3% at the end of the 1 year. (2) Many comparative studies reported that TEPR had better postoperative results in terms of early return to work, postoperative pain and chronic pain. (3,4) Another advantage of the TEPR is the access to the preperitoneal space

without intraperitoneal infiltration. Consequently, this approach minimizes the risk of damage to vital organs and port site herniation through an iatrogenic defect in the abdominal wall.

2.1. TEPR Indications:

1. Bilateral inguinal hernias
2. Recurrent inguinal hernias
3. Multipl or femoral hernias
4. Unilateral inguinal hernias

2.2. TEPR Contraindications:

1. Massive scrotal hernia
2. History of radiation to the inguinal region
3. Lower midline incision
4. Patients that can't get general anaesthesia

3.1. Advantages of Laparoscopic hernia repairs:

1. Less postoperative pain compared to classical methods.
2. Being able to leave the hospital earlier.
3. Starting all kinds of physical activities earlier.
4. Very low morbidity in terms of wound healing.
5. With laparoscopy hernia areas can be seen better, the hernia type can be determined more easily.
6. It provides safer and more effective repair in recurrent hernias.
7. It provides a safer and more effective repair in bilateral hernias.
8.It has cosmetic superiority.
9. Less postoperative analgesic use.

3.2. Disadvantages of videoscopic repair:

1- More expensive and has long learning curve than the classical method.

2- Requires laparoscopy training, certain experience and needs a long learning curve.

3- The risk of pneumoperitoneum and intraperitoneal adhesions.

4. Tools used in TEPR

Trocars: Three trocars are necessary and sufficient for TEPR. As camera enterance, trocar with 10 mm diamater is applied infraumbilically with slightly

oblique incision, balloon trocars as commercial or hand-made or telescopic method without baloon were used to create extraperitoneal space.

Two 5 mm trocars to use stapler for mesh fixation

One should be entered over the pubis. The 5 mm trocar to be used for the third and assistant. It is entered between the camera and the suprapubic trocar.

Telescope: 30º angle is needed.

Manipulation Tools (Figure 1)

a) Grasper and dissector

b) Electrocautery and scissors

c) Suction equipment

d) Endoclip

e) Prosthetic mesh: Videoscopic hernia repair techniques require the use of prosthesis. Prosthesis use has advantages such as no tension and low recurrence. Today, Nonabsorbable, monofilament polypropylene (prolene) mesh,is the most ideal and most widely used prosthetic material. 15x10 cm in size is enough to cover all potential hernia areas.

f) Veress needle needed to desufflete accidental pneumoperitoneum.

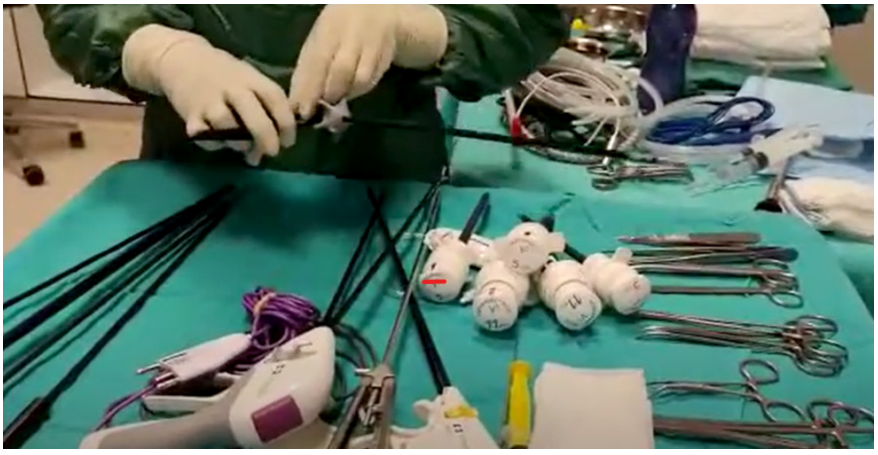

Figure 1: Various tools as dissectors, graspers, trocars, energy devices and prolene mesh used in the TEPR procedure.

5.1. Totallly Extra Peritoneal Repair Technique

Operation is performed under general anaesthesia. Patient lies in supine, slightly trendelenburg positon and both arms should be tucked. Emptying the

bladder before the operation through ürination or foley catheterisation in order not to narrow the preperitoneal space required. In Figure 2, the basic anatomic anatomy from the preperitoneal space in the inguinal area structures are shown.

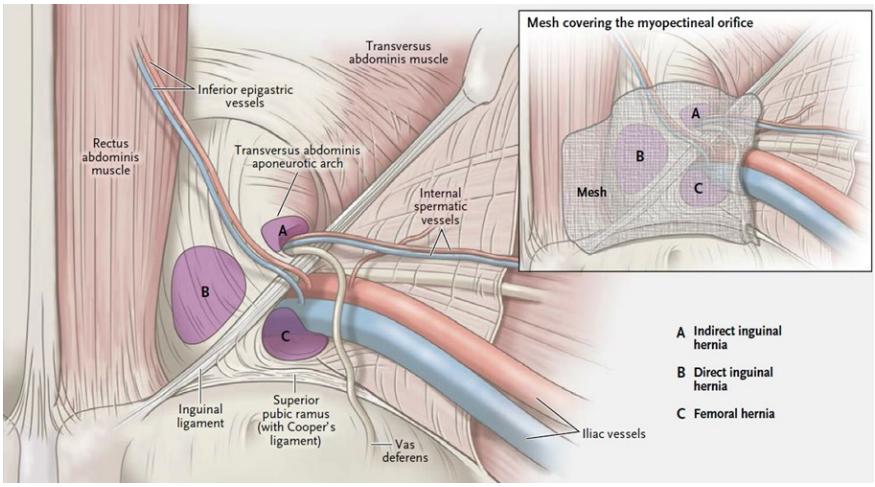

Figure 2: The anatomy of preperitoneal space

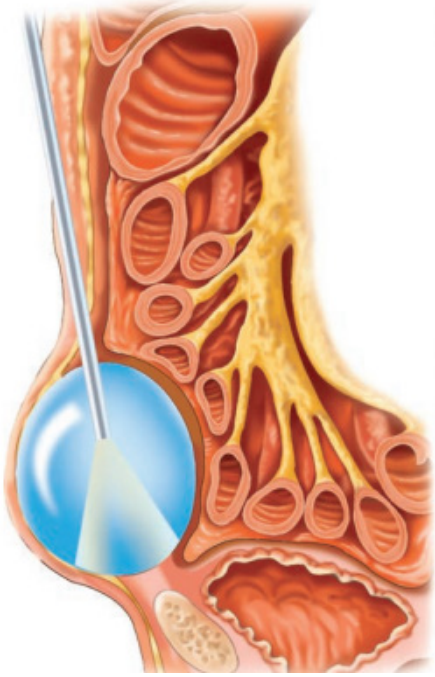

Figure 3: Baloon dissection in preperitoneal space

5.2. Settlement in the Operations Room

The monitor is placed at the foot of the patient. Surgeon to opposite side of hernia, assistant opposite the surgeon, the nurse sits to the left of the assistant. (Figure 4)

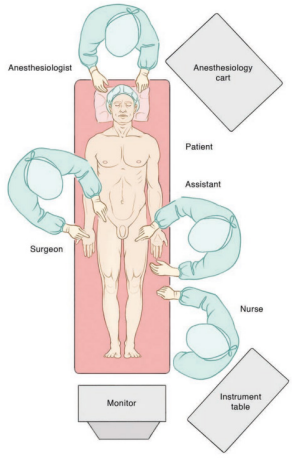

Figure 4: Surgical team set up in laparoscopic inguinal surgery

5.3. Formation of preperitoneal space

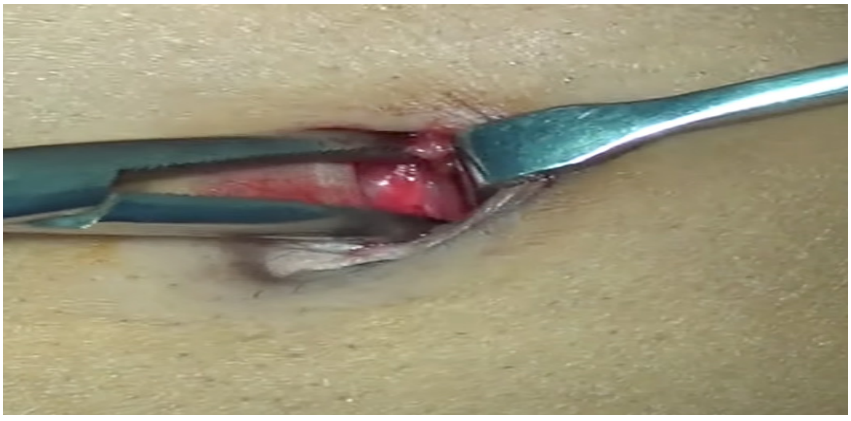

Figure 5: 12 mm infraumbilical oblique incision and opening anterior rectus fascia

Trocar entries are featured in this section. The first trocar entry is below the umbilicus through a 10-12 mm skin incision. (Figure 5) The purpose of the first trocar entry is to pass the anterior sheath of the rectus abdominus muscle and

after retracting rectus muscle laterally, the posterior sheath is to be reached. The beginning of the tunnel is prepared by inserting a finger over the the posterior sheath to enter the preperitoneal working space.

There are two methods for creating extraperitoneal space. (Figure 4) First one is the anterior sheath of the rectus abdominus muscle is suspended. Then, a 10 mm incision was made laparoscopic trocar with blunt tip probe by inserting into the created tunnel. The trocar and insufflating the gas. It is advanced preperitoneally to the inguinal region through it.

The balloon trocar is inserted through the tunnel mouth, and with gentle twisting movements. (Figure 3) The symphysis is directed towards the pubis, and the necessary space for surgery is created. In unilateral hernias, the trocar cannula should be held towards the side of the hernia, and in the midline in bilateral cases. Balloon begins to inflate. It is necessary to squeeze an average of 30 times. (Figure 3) seen first is pubic. Balloon dissection is continued until the Cooper ligament is visible. inflated balloon It is kept swollen for an average of 3 minutes, which provides hemostasis.

After the area is created, the balloon trocar is removed and gas from the same inlet. A Hasson trocar is placed to prevent its exit. Then the insufflator hose Hasson Extraperitoneal space created up to 8-12 mmHg pressure by connecting to the trocar tap is inflated. When inserting the other two trocars into the preperitoneal inguinal space, there are two different applications in terms of points. In the first application, which is mostly adopted; A 5 mm trocar is one finger above the pubic symphysis, another 5 mm trocar is between the umbilicus and the pubis from the middle (same median line in both trocars) (Figure 6). Some surgeons prefer in the second application, a 5 mm trocar was inserted suprapubic, while a 5 mm trocar hernia around, slightly below the horizontal line of the umbilicus, from the outer edge of the rectus muscle and from a point is entered. (Figure-6)

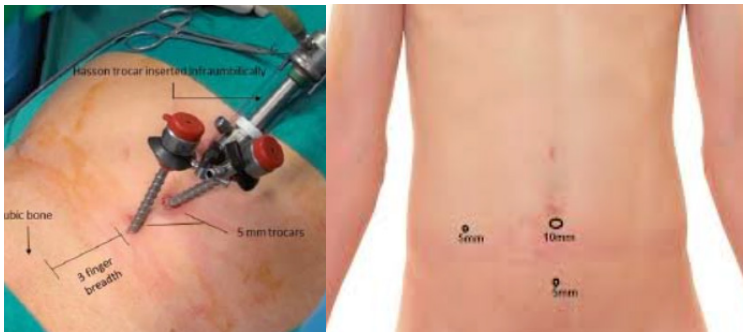

Figure 6: Port placements

5.4. Dissection of Preperitoneal area and Hernia Sac

In the principle of technique, the hernia sac formed from the peritoneum should be reduced and the mesh is fixed anterior to the hernia sac. All necessary anatomical structures should be revealed. Spermatic cord with blunt dissection at the level of the anulus inguinalis profundus after separating from the iliac vessels behind it.

The indirect hernia sac is placed antero-medial side of the spermatic cord. Testicular veins course on the posterolateral side of the sac and the vas deference course on the medial side of the indirect hernia sac. Hernia sac is captured with a grasper and dissected as much as possible by blunt dissection. If hernia sac is small, it can be left in the preperitoneal space or the distal part is excised by ligating with an endoclip. On the other hand, in large indirect hernia sacs, the excess can be cut after the sac is tied with suture.

Another option is to cut the sac at the level of the inner ring and tie the proximal part and leave the distal part in place. Especially large indirect scrotal hernias, this process is inevitable.

During the TEPR procedure, manipulation and use of tackers in the Doom triangle of Zone 3 where the femoral artery and vein are placed should be avoided. (Figure-7) Direct hernias (hasselbach's triangle) are in the medial inguinal fossa and indirect hernias are located in the lateral inguinal fossa, the epigastric vessels are the borderline between them. The femoral canal lies below the iliopubic tract and just medial to the femoral vessels.

5.5. Mesh Placement:

Mesh fixation could be done but not obligatory, especially in TEPR. Mesh fixation is especially recommended for huge hernias, mainly for direct ones due risk of mesh displacement into large hernia defect.

If the surgeon prefers on fixation with tackers or manuel suturing recommendations are: Avoid bone structures to reduce the risk of chronic osteitis; Avoid tacking epigastric vessels and do not fixate below the iliopubic tract over triangle of pain or Doom. Consider at least 2 cm above the iliopubic tracts and five to six fixations are enough to keep the mesh in proper position (higher attachment numbers will increase the possibility of chronic pain). A bimanual technique should be used to palpate the abdominal wall while placing a penetrating fixation.

Proper preperitoneal dissection and correct mesh positioning are vital to obstacle recurrence and mesh complications other than fixing the mesh regardless of material.

5.6. Anatomy of Preperitoneal space

The understanding of the anatomy of the preperitoneal space and posterior abdominal wall seems to be essential to a proper posterior approach. Furtado et al. in their original article published at 2019 has reported a new way to understand the anatomy of the groin in posterior view. (5) With the visualisation of simple landmarks and some anatomical triangular areas, it becomes easy to define and conduct the dissection plans.

The definition of 'Inverted Y and 5 Triangles' as defined by Furtado et al. (5) When the dissection is completed in laparoscopic inguinal hernia surgery, epigastric vessels, spermatic vessels and Ductus deferens (Ligamentum teres uteri lateral round ligament in women) are anatomically revealed in figure 8,9. Here, an inverted Y appears: the leg of the inverted Y is formed by the epigastric vessels, and its arms by the spermatic vessels and the Ductus deferens. Here, when you pass a virtual iliopubic tract tangentially from the junction of the arms and legs, which is the midpoint of this inverted Y, which is anatomically exactly the same; 5 triangles appear shown in figure 9. Let's describe these triangles:

1. Triangle of Doom: The area between the ductus deferens and the spermatic vessels.
2. Triangle of Pain: The area between the gonadal vessels, the iliopubic tractus and the peritoneum.
3. Indirect hernia triangle: The area above the iliopubic tract, lateral to the epigastric vessels.
4. Direct hernia triangle: The area above the iliopubic tract, medial to the epigastric vessels.
5. Femoral hernia triangle: The area medially under the iliopubic tract, medial to the ductus deferens.

Again, detailed in this article; As shown in figure 7, the definition of Zone has entered the surgical anatomy terminology in laparoscopic inguinal hernia repair and its use is becoming widespread. As can be seen in the article; 3 zones are defined. Zone 1, Zone 2 and Zone 3. Anatomical scopes are as follows:

Zone 1 – We can call it the Bogros, the area lateral to the spermatic vessels. It also includes the pain triangle.

Zone 2 – The ductus deferens or, in females, the region medial to the Ligamentum teres uteri. Some also call it the Retzius region. There are also those who call it the Bendavid region.

Zone 3 – The area starting from the epigastric vessels and between the ductus deferens and the spermatic vessels. Contains the triangle of Doom.

In their recent publication, Daes and Felix proposed the stepwise approach to perform laparoscopic hernia repair safely and efficiously. (6) Furtado Marcelo and Edward Felix were reported 10 golden rules for all laparoscopic herni surgeries. (7)

These ten rules:

1. In TEPR, blunt dissection with a direct telescope or dissection of the first cavity with the use of a balloon trocar appears to be equally effective.

2. The adipose tissue in the preperitoneal space should be sweft from the peritoneum toward the abdominal wall. To avoid damage to the epigastric vessels or injury to the nerves in Zone 1, the transversalis fascia and muscles should be intact. Opposite to open approach, nerves should not be dissected or identified in TEPR to decrease the exposure of these nerves to the foreign body reaction and the probability of chronic groin pain. During TEPR procedure, Zone 2 is dissected initially by blunt dissection with a balloon trocar or telescope, then Zone 1 and Zone 3 are dissected. Dissection of the central zone (Zone3) is performed after Zone1 and 2 because of the fact that that is the most difficult part of the operation due to the variable structural anatomy. At this stage of dissection, injuries to the ductus deferens or gonadal vessels and ruptures of peritoneum may occur with high probability.

3. The dissection preperitoneal space must done minimum 20 mm below the cooper ligament and pubis in Zone 2 to place a sufficiently large mesh that overlaps the Femoral and direct hernia space by at least 3–4 cm below.

However, the risk of bladder injury should not be forgotten. If present, the hernia sac is dissected directly and the content of the hernia is reduced. The fascia transversalis is dissected and held distally. When dissecting a direct hernia, the surgeon should stay on the right plane not to damage the bladder. The bladder must be emptied before the operation begins. A full bladder can reduce the surgical area and make dissection difficult. Bladder catheterization is not routinely needed if the patient empties the bladder before the theatre. There is no consensus on suturing or plication of the fascia transversalis in direct hernia cases.

4. In zone 3, missed femoral hernia should be searched through dissection of the external iliac vein. Attention should be paid to the Femoral lymph nodules

should be differentiated from the preperitoneal fatty tissue extending from the external iliac vein to the femoral canal to avoid bleeding.

5. The peritoneum of hernia sac should be dissected inferiorly until the level where the ductus deferens crosses the iliac vein and the iliopsoas muscle is seen posteroinferiorly at first zone. Dissection of the indirect hernia sac in zone 3 is the most challenging step in hernia repair. During dissection of the indirect sac, the sac should be mobilized in both sides to facilitate identification of the ductus deference and gonadal vessels of the cord. Thus, injuries that may occur in the area of Doom can be reduced. (Figure 10)

In females, the ligamentum teres uteri is usually firmly attached to the peritoneum. It is recommended to cut the ligament at least 1 cm proximal to the internal ring to protect the genital branch of the genitofemoral nerve near here.

6. In complete indirect hernias, it is recommended to cut and leave the distal hernia sac inside as in open repair. An indirect hernia sac is usually cut through the inguinal canal and reduced. Large hernial sacs (especially chronic-fibrotic ones) can be excised only after they have safely identified the structures of the spermatic cord. This decision is made in order to avoid excessive dissection of the cord elements and thus prevent their injury. Postoperative hydrocele is easier to deal with than scrotal hematoma, ischemic orchitis, or spermatic cord injury.

7. The internal ring should be investigated during Zone 3 dissection to look for a cord lipoma.The cord lipoma is the retroperitoneal fat, usually extending with the structures of the cord in the annulus inguinalis profundus region. Lipoma cannot be seen with. simple visual inspection of the annulus inguinalis profundus. Any lipomatous soft tissue should be dissected and removed from the inguinal canal. Untreated lipomas are the main cause of bulging after TEPR. Total removal is not absulately recommended but must be placed over the mesh to prevent folding of the mesh. Visualization of the iliopubic tract is a good indication that whether there is lipoma or not.

8. At least 10×15 cm mesh should be placed to cover the myopectineal arifice (Indirect, Direct and Femoral triangles) extending 4 cm more. The peritoneum should not be left behind the mesh to prevent folding and/or rolling during gas evacuation or peritoneal closure.

9. Mesh fixation is not required in TEPR. Mesh fixation is recommended for large inguinal hernias, especially direct hernias. If the surgeon decides on fixation with tackers, recommendations are: Avoid bone structures: thus the risk of chronic osteitis is reduced; Avoid infused epigastric vessels. Do not fixate below the iliopubic tract. Consider at least 2 cm above. five to six fixation points

are sufficient to fix the mesh (more fixation numbers may result in increased risk of chronic pain). A bimanual technique should be used to palpate the abdominal wall while placing a penetrating fixation.

It should be known that fixing the mesh regardless of material does not prevent problems with insufficent dissection or mesh positioning.

10. In TEPR, while dessuflating the preperitoneal space, the caudal part of the preperitoneal mesh can be pressed down with the help of a grasper to prevent the peritoneum from folding or rolling in the caudal part of the mesh. When the peritoneum re-expands and the mesh moves at the end of the TEPR procedure, further dissection is required.

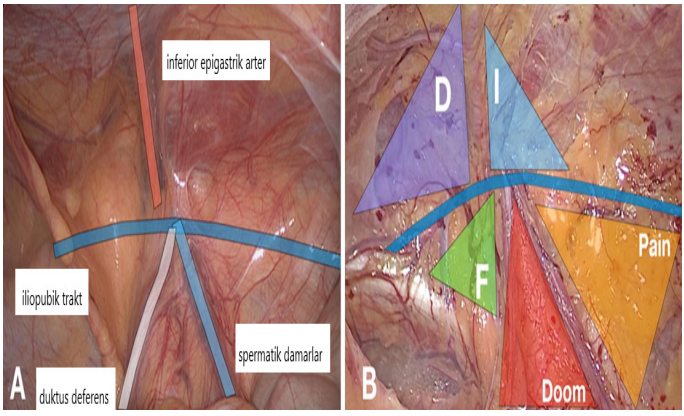

Figure 8: Inverted Y and Five triangles. (7)

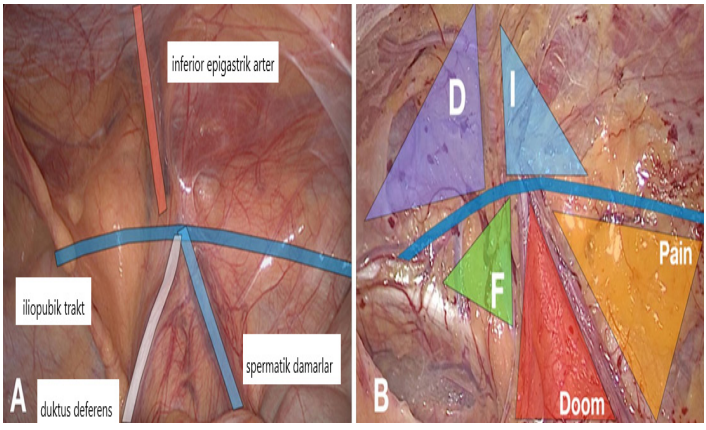

Figure 9: Important triangles in preperitoneal space. (7)

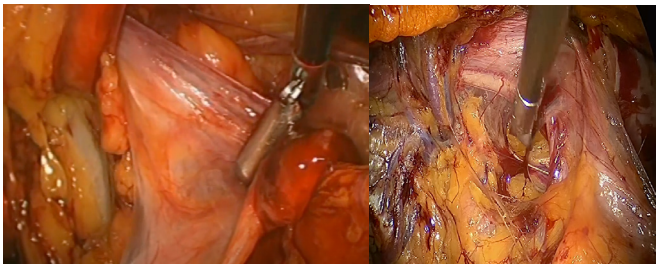

Figure 10: Dissection of spermatic cord and indirect sac

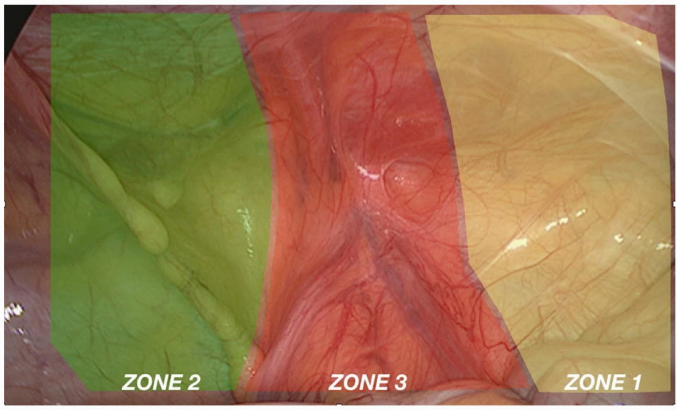

Figure 7: Three zones in posterior abdominal Wall. (7)

6. Complications of TEPR

Overall complication rates in literatüre vary 2%-24%. (8, 9) All possible complications of TEPR are listed in Table 1.

Complications of TEPR can be divided into:

- Intraoperative
- Postoperative.

6.1. Intraoperative complications and precautions:

6.1.1 Peritoneal tears:

This complication may ocur in any part of the procedure as during the creation of Preperitoneal Space or dissection of the hernia sac. While entering the Preperitoneal Space, widened linea alba may result in accidental tearing in the peritoneum; in this condition closing the rectus defect and incising the sheath more laterally will probably solve the problem. There are some Improper placement of balloon trocar may cause the dissection of muscle fibers. Entry

into peritoneum will cause pneumoperitoneum. Rupture of the balloon in preperitoneal space may result from excessive insufflation of baloon or improper place of baloon. Ten mm camera trocar must placed into the tunnel to avoid Carbondioxide gas leakage.

To avoid these, one must ensure that the balloon is made properly and the preperitoneal space is entered by retracting the rectus muscle laterally to visualize the posterior rectus sheath. Also, the balloon trocar is inserted gently, with 30 degree angle to the skin, to avoid tearing the peritoneum. Inflation of the baloon must be done slowly with saline to ensure smooth and even distention and prevent its rupture.

6.1.2. Bladder Injuries:

This complication is less common than bowel injuries. The injury is commonly seen in anterosuperior area of bladder associated with 5 mm suprapubic trocar entry, direct or sliding hernia dissection. Perioperative distention of bladder and perivesical adhesions seems to be the main reasons of injury. It is advisable that beginners catheterize the bladder during the initial part of their learning curve. When encountered during the operation, surgeon may try to repair the defect laparoscopically with two suturing layers with absorbabl sutures and 1 to 2 weeks urine cathetrization is needed. At the end of treatment, cystogram must be taken to be sure the healing of defect.

6.1.3. Bowel injuries:

Colon and small intestines are also at risk during TEPR. (10) Colon and small bowel may be adherent to hernia sac so dissection may cause injury. Caecum, ascending colon and small bowel on right side and sigmoid colon on left side are in danger for injury. Trocar placement may cause colon or small bowel injuries especially in adherent cases. Electrocautery may also cause direct bowel injury. İf the injury is noticed during surgery, defect can be managed laparoscopically either with stapling or simple suturing. Mortality rate is higher in missed bowel injuries. (11)

6.1.4. Vascular Injuries:

The bleeding incidence during TEPR is reported to be 0.5%. (12) On the other hand, main vascular damage that must be repaired was 0,08 %. (13) Despite low prevalence, it is reported that bleeding-related mortality during TEPR is between 9% and 18%. (14). Iliac or femoral vessels are two majör vasculature that the most severe injuries usually ocur. The mechanisms of injury

are misplaced endoscopic tacker use, trocar entrance injury or direct dissection in laparoscopic repairs. In these major vascular damages, Laparatomy should be performed, and bleeding may be temporarily controlled with direct mechanical compression until vascular surgeons perform definitive control.

Inferior epigastric vessels and external iliac arteries are two most commonly injured vessels during TEPR. Obturator vein, deep circumflex iliac vessel and spermatic vein injuries are also reported. Corona mortis (Shunt between obturator vessels and external iliac vessels) bleeding can also be encountered. Most of these minor bleedings could be handled with endoclips or cautery. Other than the external iliac vessels, all vascular structures in the groin can be ligated, clipped safely.

6.1.5. Injury to Vas Deferens

Vas deferens injury during IHR is reported to be 0.4%. (15) During TEPR, infertility may result if the ductus deferens within the cord gets injured. In TEPR approach, crush injury may result from grasping the vas with various instruments. İf the vas gets transected during operation, early anastomosis by urologist should be performed. would increase the risks of mesh rejection, carcinogenesis, and inflammation. It is reported that Synthetic mesh material used in IHR causes chronic scarring which leads to vas pathologies, resulting in dysejaculation syndrome and decreased fertility rates. (16)

Minimal or no grasping and manipulation of vas deferens should be.placement, if possible, no or very little fixator should be used.

6.1.6. Pneumoperitoneum

In the literatüre, the incidence of Pneumoperitoneum during TEPR reported to be as 11–48%. (17) Putting the patient in Trendelenburg's position and decreasing the insufflation pressures to 10 mm Hg helps. If the problem still persists, a Veress needle can be inserted at Palmer's point.

6.2. Postoperative Complications

6.2.1. Hernia recurrence:

In literatüre, recurrence rates are quite variable between 4%-10.1%. (3, 18, 19) Of course many factors can be responsible as experience of surgeon and surgical team, quality of mesh and instruments used, technical sufficiency of instruments. The surgeons who will perform TEPR should be familier with the preperitoneal anatomy, the principles of operative technique and must have the advanced laparoscopic skills to reduce the recurrence rates.

In the case of bulging, pain after the surgery at the repair site, first of all recurrence, lipoma, hydrocele or seroma formation should be suspected. Physical examination and use of ultrasonography, computerized tomography or magnetic resonans imaging can clarify the diagnosis. Open Lichtenstein approach will be better and efficient in the second operation of the recurrence of Posterior TEPR.

6.2.2. Seromas:

Synthetic mesh repairs may cause fluid collections called seroma that most commonly develop within one week of TEPR in 6%-26% of cases. In some cases, large indirect sac distal part may be filled with reactionary fluid and may mimic seroma. Seromas often mimic early recurrence. Most resolve spontaneously over 4 to 6 weeks. To accelerate resolution, warm compression can be applied. Seromas should not be aspirated to avoid secondary infection. But when it cause discomfort or restrict activity for a prolonged time, drainage should be done in sterile conditions. A seroma can be avoided by minimizing dissection of cord elements, fixing the direct sac to the pubic bone, and fenestration the transversalis fascia in a direct hernia. Some surgeons put in a suction drain if there is apparent bleeding or excessive dissection.

6.2.3. Groin pain:

Osteitis pubis, meralgia paresthesia and local nerve entrapment are chronic pain syndromes that can be encountered after TEPR. At greatest, risk of entrapment is present in the genitofemoral and lateral femoral cutaneous nerves in TEPR. Injury to the lateral femoral cutaneous nerve results in meralgia paresthesia, a condition characterized by persistent paresthesia of the lateral thigh. Initial treatment of nerve entrapment consists of rest, ice, NSAIDs, physical therapy, and possible local corticosteroid and anesthetic injection. This can be followed by a trial of gabapentin (20) or its analogues. Osteitis pubis is characterized by inflammation of the pubic symphysis and usually presents as medial groin or symphyseal pain that is reproduced by thigh adduction. Avoiding the pubic periosteum when placing sutures and tacks reduces the risk of developing osteitis pubis. CT scan or MRI excludes hernia recurrence, and bone scan is confirmatory for the diagnosis. Initial treatment is identical to that of nerve entrapment; however, if pain remains intractable, orthopedic surgery consultation should be sought for possible bone resection and curettage. Irrespective of treatment, the condition often takes six months to resolve. (21)

7. The other complications:

Hydrocele, wound infection, testicular ptosis, testicular atrophy, ischemic orchitis, mesh infection, mesh rejection and mesh contraction are other complications encountered after TEP.

8. Conclusion

Several randomised controlled trials have demostrated that TEPR is superior to Open Lichtenstein repair in terms of low postoperative pain, acceptable low complication rate, low recurrence rate and early return to work. (22) Because TEPR requires specialized instruments and longer operative times, its cost is higher than open repair; however, the potential financial benefit of shorter recovery and decreased pain may offset these costs. However, proper case selection, extensive knowledge of preperitoneal anatomy, excellent surgical laparoendoscopic technique, and the surgeon's experience and expertise are the cornerstones of the best clinical outcome with low morbidity or mortality. Due to acceptable recurrence rates, TEPR is accepted as an advantageous method in the treatment of both bilateral and recurrent IH in experienced hands. Since there is no accepted perfect surgical technique suitable for all IHs, every hernia surgeon must learn, apply and offer both open and laparoendoscopic technique options to patients as the treatment modality. (23)

Hernioplasty related complications	Recurrence Hematoma Seroma Chronic pain Infertility
Laparoscopy related complications	Intestinal injuries Bladder injury Major vascular injuries Gas embolism Subcutaneous empheysema
Patient related complications	Deep venous thrombosis Mekanik or paralytic ileus Cardiopulmonary complications Urinary complaints
Mesh related complications	Rejection Folding Mesh infection Mesh erosion

Table 1: TEPR procedure complications

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CHAPTER II

MANAGEMENT OF APPENDİCEAL NEUROENDOCRINE NEOPLASMS (ANENS)

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1. Introduction

Appendiceal Neuroendocrine Neoplasms (ANENs) represent a unique and heterogeneous group of tumors that originate in the appendix, a relatively small organ often overshadowed by its larger gastrointestinal counterparts. Despite their rare occurrence, ANENs pose diagnostic and therapeutic challenges that require a comprehensive understanding of their clinical behaviors and optimal management strategies. Appendiceal neuroendocrine neoplasms (ANENs) are a diverse group of malignancies that account for a notable percentage of primary tumors arising in the appendix, with reported incidence rates ranging from 25% to 60%. (1) Frequently, these neoplasms are incidentally discovered during appendectomies performed for acute appendicitis, constituting a prevalence of 0.16% to 2.3% in such cases. (2) ANENs exhibit a predilection for diagnosis towards the latter part of the second decade of life, with a notably higher occurrence in females. (3)

The current World Health Organization (WHO) histological classification recognizes ANENs as a heterogeneous entity encompassing well-differentiated neuroendocrine tumors (NETs), poorly differentiated neuroendocrine carcinomas (NECs) that can manifest as large cell or small cell types, and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs). (4) This classification reflects the complexity of ANENs and their varied clinical presentations, demanding a multidisciplinary approach to their management.

This chapter aims to provide an in-depth exploration of ANENs, covering various aspects of their diagnosis and treatment. From the initial clinical presentation and diagnostic tools to surgical approaches, post-surgical evaluations, and therapies for metastatic disease, we will delve into the intricacies of managing ANENs. Additionally, we will examine the significance of a multidisciplinary approach in determining the most suitable treatment for these patients.

ANENs exhibit a broad spectrum of behaviors, ranging from indolent, well-differentiated tumors to highly aggressive poorly differentiated carcinomas. This heterogeneity underscores the importance of personalized care and the need for healthcare providers to collaborate closely with experts in the field of neuroendocrine tumors (NETs).

The recent advances in our understanding of NETs, coupled with the emergence of novel therapeutic options, have improved the outlook for patients with ANENs. However, it is vital to recognize the nuances of these tumors, such as their somatostatin avidity, histological grade, and tumor burden, in order to select the most appropriate treatment strategies.

As we navigate through the landscape of ANENs, we will emphasize the significance of multidisciplinary discussions, the evolving role of various therapeutic modalities, and the need for ongoing research to further enhance our management approaches. The following sections will provide a detailed exploration of ANENs, offering insights and guidance for healthcare providers and researchers dedicated to improving the care and outcomes of patients with these unique neoplasms.

2. Classification

According to update in September 2021, the World Health Organization (WHO) classification system for neuroendocrine neoplasms (NENs), including appendiceal neuroendocrine neoplasms (ANENs), categorizes these tumors based on their histological and pathological characteristics. (5-7)

2.1. Well-Differentiated Neuroendocrine Tumors (NETs):

- NET G1: Well-differentiated tumors with a low proliferation rate (Ki-67 index $\leq$ 2%) and confined to the mucosa or submucosa of the appendix.

- NET G2: Well-differentiated tumors with a low to intermediate proliferation rate (Ki-67 index 3-20%) or tumors extending beyond the submucosa but still confined to the appendix.

- NET G3: Well-differentiated tumors with a high proliferation rate (Ki-67 index > 20%) or tumors with invasion beyond the appendix wall.

2.2. Poorly Differentiated Neuroendocrine Carcinomas (NECs):

These are high-grade neuroendocrine tumors with a more aggressive clinical course. They may resemble small cell or large cell carcinomas and are often treated more like small cell lung cancer. Ki-67 index is typically high (usually >20%). These tumors are high grade.

- NEC G1: Well-differentiated tumors with a low proliferation rate (Ki-67 index ≤ 2%) and confined to the mucosa or submucosa of the appendix.
- NEC G2: Well-differentiated tumors with a low to intermediate proliferation rate (Ki-67 index 3-20%) or tumors extending beyond the submucosa but still confined to the appendix.
- NEC G3: Well-differentiated tumors with a high proliferation rate (Ki-67 index > 20%) or tumors with invasion beyond the appendix wall.

2.3. Mixed Neuroendocrine-Non-neuroendocrine Neoplasms (MiNENs):

These tumors have a combination of neuroendocrine and non-neuroendocrine components. MiNENs can be further classified based on the predominant component and its grade. For example, if the neuroendocrine component is poorly differentiated, it is classified as a MiNEN with a high-grade NEC component. Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) of the appendix are exceptionally rare tumors that contain both neuroendocrine and non-neuroendocrine components. These tumors are challenging to diagnose and treat due to their complex nature. MiNENs of the appendix typically consist of a combination of well-differentiated neuroendocrine tumor (NET) and non-neuroendocrine carcinoma components. The diagnosis of MiNENs of the appendix relies on histopathological examination of the tumor tissue. Specialized staining techniques, such as immunohistochemistry, may be necessary to confirm the presence of both neuroendocrine and non-neuroendocrine components. Each component (neuroendocrine and non-neuroendocrine) is graded separately based on its histological characteristics. The grading helps determine the degree of differentiation and aggressiveness of each component. The prognosis of MiNENs of the appendix can vary depending on several factors, including the grade and stage of each component. Typically, the behavior of the neuroendocrine component plays a significant role in overall

prognosis. High-grade neuroendocrine components (NECs) are associated with a poorer prognosis. Managing MiNENs of the appendix is complex and often requires a multidisciplinary approach. Treatment decisions are based on factors such as the stage, grade, and extent of the tumor. Surgical resection is a common approach for localized disease, but additional therapies such as chemotherapy or targeted therapies may be considered, particularly for high-grade NEC components. MiNENs of the appendix are rare, and research in this area is ongoing. Classification criteria and treatment guidelines may evolve as more is learned about these tumors.

3. Clinical Presentation

3.1. Incidental Discovery

Many ANENs are asymptomatic and are discovered when the appendix is removed during surgery for unrelated conditions like acute appendicitis. This incidental finding highlights the importance of careful pathological examination of appendix specimens. (8, 9)

3.2. Abdominal Pain:

Patients with ANENs may experience abdominal pain or discomfort, which can be localized to the lower right abdomen. This pain can mimic the symptoms of acute appendicitis. (10)

3.3. Carcinoid Syndrome:

In some cases, ANENs may produce hormones such as serotonin, leading to carcinoid syndrome. This syndrome is characterized by flushing of the skin, diarrhea, wheezing, and heart valve abnormalities. It is more commonly associated with midgut neuroendocrine tumors but can occur with ANENs. (11)

3.4. Obstruction:

Large ANENs or those with extensive local invasion can cause intestinal obstruction, leading to symptoms like abdominal distension, nausea, and vomiting. (12)

3.5. Appendiceal Mass:

Rarely, ANENs can present as palpable masses in the lower right abdomen.

4. Diagnostic Approaches

4.1. Imaging Studies

Various imaging modalities can provide valuable information. Computed Tomography (CT) scans, Magnetic Resonance Imaging (MRI), and ultrasound can help visualize the tumor, evaluate its size, and detect any metastatic lesions. Imaging studies play a crucial role in the diagnosis, staging, treatment planning, and monitoring of patients with appendiceal neuroendocrine neoplasms (ANENs). These studies help healthcare providers visualize tumors, assess their size and extent, and track changes over time.

4.1.1. CT Scans (Computed Tomography)

CT scans are often the initial imaging modality used to evaluate ANENs. They provide detailed cross-sectional images of the abdomen and pelvis, helping to identify tumors, assess their size, and detect any spread to nearby lymph nodes or organs. Contrast dye may be used to enhance the images.

4.1.2. MRI (Magnetic Resonance Imaging)

MRI scans use strong magnetic fields and radio waves to create detailed images of the abdomen and pelvis. MRI is valuable for assessing soft tissue structures and can provide information about tumor characteristics and involvement of nearby structures.

4.1.3. PET Scan (Positron Emission Tomography)

PET scan can help determine the metabolic activity of ANENs and their metastases. A radiolabeled glucose analog is injected into the patient's bloodstream, and areas with high metabolic activity, such as cancer cells, are detected by the PET scanner. Combined with CT (PET-CT), this imaging modality provides both anatomical and functional information. (13)

4.1.4. Octreotide Scintigraphy (Somatostatin Receptor Scintigraphy)

Octreotide scintigraphy is a nuclear medicine imaging technique involves injecting a radioactive substance linked to a somatostatin analog. Neuroendocrine tumors, including ANENs, often express somatostatin receptors. The radioactive substance binds to these receptors, allowing the detection of tumor sites. This imaging method is particularly useful for identifying somatostatin receptor-positive tumors. Somatostatin receptor scintigraphy (SRS), also known

as octreotide scintigraphy or somatostatin receptor imaging, is a valuable nuclear medicine imaging technique used in the diagnosis and management of neuroendocrine tumors (NETs). SRS is based on the fact that many neuroendocrine tumors, including ANENs, express somatostatin receptors on their cell surfaces. Somatostatin is a hormone that can inhibit the secretion of various hormones and has antiproliferative effects. In SRS, a radioactive compound linked to a synthetic somatostatin analog is administered to the patient. This compound is designed to bind to somatostatin receptors on the tumor cells. A radiopharmaceutical, typically Indium-111 pentetreotide (Octreoscan) or Gallium-68 DOTATATE, is injected into the patient's bloodstream. The radiopharmaceutical contains a radioactive isotope (Indium-111 or Gallium-68) linked to a somatostatin analog. Over time, the radiopharmaceutical circulates through the bloodstream and binds to somatostatin receptors on the surface of neuroendocrine tumor cells. Several hours after the injection (usually around 4-6 hours), the patient undergoes whole-body imaging using a gamma camera equipped with a collimator. This camera detects gamma rays emitted by the radioactive compound bound to the tumor cells. The images obtained during the scan are analyzed by nuclear medicine specialists. Areas of increased radioactivity indicate the presence of somatostatin receptor-positive tumors. Somatostatin receptor scintigraphy has several clinical applications in the management of ANENs and other NETs: SRS helps confirm the presence and location of neuroendocrine tumors, including ANENs, based on the detection of somatostatin receptor expression. SRS assists in determining the extent and distribution of tumor involvement, including the identification of primary and metastatic lesions. The scan provides information about the density and distribution of somatostatin receptors on tumor cells. This information is crucial for selecting patients who may benefit from somatostatin analog therapy. SRS can guide treatment decisions, including the choice of somatostatin analog therapy, targeted radionuclide therapy (PRRT), or other therapies based on receptor status and tumor burden. SRS is used for monitoring treatment response and disease progression in patients with ANENs and other NETs. (14)

4.1.5. Endoscopic Ultrasound (EUS)

EUS combines endoscopy with ultrasound imaging. A specialized endoscope is inserted into the gastrointestinal tract to obtain high-resolution ultrasound images of the appendiceal region and nearby lymph nodes. EUS can help assess tumor size, invasion depth, and lymph node involvement.(15)

4.1.6. Angiography

Angiography involves injecting a contrast dye into blood vessels to visualize the blood supply to tumors. This technique can be valuable for planning surgery or other interventions to treat ANENs.

4.2. Biopsy and Pathology

The tissue obtained from the biopsy or surgical resection is sent to a pathologist for detailed examination. Pathology provides critical information about the nature of the tumor, including its type, grade, and stage. The pathologist examines the tissue under a microscope to determine the histological classification. ANENs are typically categorized as well-differentiated (low-grade) or poorly differentiated (high-grade) neuroendocrine neoplasms. Well-differentiated ANENs are further classified into typical carcinoid, atypical carcinoid, or neuroendocrine tumor, grade 1 (NET G1) based on specific criteria. Grading assesses the degree of differentiation and proliferation of tumor cells. Grading is essential for determining the prognosis and guiding treatment decisions. The Ki-67 index, which measures the percentage of proliferating (actively dividing) tumor cells, is often used for grading. A low Ki-67 index is associated with well-differentiated ANENs (G1 or G2), while a high Ki-67 index suggests poorly differentiated ANENs (G3). Staging evaluates the extent of tumor spread. For ANENs, staging is primarily based on tumor size, extent of invasion, and the presence of regional lymph node involvement. The staging system for ANENs may follow guidelines established for other neuroendocrine tumors (e.g., TNM staging) and is important for treatment planning.

4.3. Immunohistochemistry

Immunohistochemistry (IHC) is a crucial laboratory technique used in pathology to detect specific proteins in tissue sections. In the context of diagnosing and characterizing appendiceal neuroendocrine neoplasms (ANENs), IHC plays a significant role in confirming the presence of neuroendocrine markers and providing additional information about the tumor's characteristics. Here's how IHC is applied in the evaluation of ANENs:

4.3.1. Neuroendocrine Marker Expression

IHC is used to determine whether the tumor cells express neuroendocrine markers. Common neuroendocrine markers include chromogranin A,

synaptophysin, and CD56 (neural cell adhesion molecule). These markers are proteins that are typically expressed in neuroendocrine cells. Positive staining for these markers indicates the neuroendocrine nature of the tumor.

4.3.2. Proliferative Index

Ki-67 is another marker commonly assessed through IHC. Ki-67 is a protein associated with cell proliferation, and its expression can help determine the tumor's growth rate. A higher Ki-67 index suggests a more aggressive tumor, while a lower index indicates a slower-growing, less aggressive tumor.

4.3.3. Grading

IHC results, particularly for chromogranin A and Ki-67, can aid in tumor grading. Grading classifies tumors into different grades (G1, G2, G3) based on their cellular characteristics, including differentiation and proliferation rate. Well-differentiated ANENs with low proliferation rates are typically classified as G1 or G2, while poorly differentiated ANENs with high proliferation rates are classified as G3.

4.3.4. Somatostatin Receptor Expression

IHC can be used to assess the expression of somatostatin receptors (SSTRs) on the surface of tumor cells. This information is essential for deciding whether somatostatin analog therapy, a common treatment option for NETs, is likely to be effective. SSTR expression can also be assessed through molecular imaging studies like Ga-68 DOTATATE PET scans.

4.3.5. Other Markers

Depending on the specific characteristics of the tumor and the clinical context, other IHC markers may be used to gather additional information. These markers might include markers of differentiation, hormonal production (e.g., insulin, gastrin), and markers that help distinguish between appendiceal NETs and other types of gastrointestinal tumors.

4.3.6. Tumour Localization

In some cases, IHC can assist in localizing the primary tumor site, especially when metastatic lesions are identified. Markers that are specific to certain primary sites, such as the pancreas or small intestine, can help identify the origin of the tumor. (16-17)

4.4 Endoscopy

Endoscopy plays a significant role in the diagnosis, staging, and management of appendiceal neuroendocrine neoplasms (ANENs), although its role is relatively limited compared to other gastrointestinal conditions. Here are some ways in which endoscopy can be involved in the evaluation and management of ANENs (15)

4.4. Tumour Markers

Tumor markers for appendiceal neuroendocrine neoplasms (ANENs) are not as well-defined or standardized as those for some other types of cancer. The diagnostic and prognostic value of specific tumor markers in ANENs may vary, and there isn't a single universally accepted tumor marker associated with ANENs. However, there are certain markers that may be assessed in the context of ANENs: (18,19)

4.5.1. Chromogranin A

Chromogranin A (CgA) is a general neuroendocrine marker and may be elevated in ANENs. It is commonly used as a marker for the presence of neuroendocrine tumors but is not specific to ANENs.

4.5.2. Synaptophysin

Synaptophysin is another general neuroendocrine marker, and like CgA, it is not specific to ANENs. Elevated synaptophysin levels can indicate the presence of neuroendocrine differentiation.

4.5.3. Pancreatic Polypeptide (PP)

PP is produced by some neuroendocrine tumors, including those arising in the appendix. Elevated PP levels may be associated with ANENs.

4.5.4. Neuron-Specific Enolase (NSE)

NSE is produced by neuroendocrine cells and may be used as a marker in the evaluation of neuroendocrine neoplasms, including ANENs.

4.5.5. Serotonin (5-Hydroxytryptamine or 5-HT)

ANENs, especially those with carcinoid features, may produce serotonin. Elevated serotonin levels can be associated with carcinoid syndrome, a condition characterized by flushing, diarrhea, and other symptoms. Serotonin levels can be

measured in the blood and urine. Elevated levels of serotonin and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in the urine or blood may suggest the presence of a neuroendocrine tumor, including ANENs.

4.5. Genetic Testing

Genetic testing can play a crucial role in the assessment and management of appendiceal neuroendocrine neoplasms (ANENs), especially when dealing with well-differentiated tumors or mixed neuroendocrine neoplasms (MiNENs). Here are some aspects of genetic testing in ANEN:

4.6.1. Identification of Genetic Mutations

Genetic testing can help identify specific genetic mutations or alterations that may be driving the growth and behavior of ANENs. Common mutations found in neuroendocrine tumors (NETs) and MiNENs include those affecting genes like MEN1, DAXX, ATRX, and mTOR pathway genes (e.g., TSC2).

4.6.2. Differentiation of ANEN Subtypes

Genetic testing can aid in distinguishing between different subtypes of ANENs, such as those with purely neuroendocrine features and those with mixed histology. This differentiation can be valuable for treatment decisions and prognostication.

4.6.3. Therapeutic Implications

Identifying specific genetic mutations can have therapeutic implications. Some targeted therapies are available for NETs with specific mutations. For example, mTOR inhibitors like everolimus may be used in cases with mTOR pathway mutations.

4.6.4. Prognostic Information

Genetic testing results can provide insights into the potential aggressiveness of the tumor and help with prognostication. Some genetic alterations are associated with a more favorable or unfavorable prognosis.

4.6.5. Familial Screening

When genetic mutations associated with ANENs are identified in a patient, it may warrant genetic screening of family members to assess their risk and consider early detection measures.

4.6.6. Treatment Decision-Making

Genetic testing results can influence treatment decisions. For instance, if a specific mutation is identified, targeted therapies may be considered as part of the treatment plan.

5. Surgical Management of Appendiceal Neuroendocrine Neoplasms (ANENs)

Surgical management plays a central role in the treatment of Appendiceal Neuroendocrine Neoplasms (ANENs). The approach to surgery for ANENs varies based on factors such as tumor size, location, grade, and the presence or absence of metastasis. In this section, we will delve into the surgical strategies employed in the management of ANENs.

Surgical resection the treatment of appendiceal neuroendocrine tumors (ANETs) can vary depending on the size of the tumor. Here's an outline of potential treatment approaches based on tumor size:

5.1. Small Tumors (Less than 1 cm):

- Surgery (Appendectomy): Small ANETs, especially those that are well-differentiated and confined to the appendix, may be effectively treated with a simple appendectomy, which involves removing the appendix.

5.2. Intermediate-Sized Tumors (1-2 cm):

- **Surgery (Appendectomy or Right Hemicolectomy):** The treatment approach for intermediate-sized tumors depends on several factors, including histological grade, invasion, and lymph node involvement. If the tumor is well-differentiated, localized, and hasn't invaded surrounding tissues, an appendectomy may still be considered. However, if there are concerning features, a right hemicolectomy (removal of the cecum and a portion of the colon) might be recommended.

5.3. Large Tumors (Greater than 2 cm):

- **Surgery (Right Hemicolectomy):** Larger ANETs typically require more extensive surgery, such as a right hemicolectomy, to ensure complete removal. This approach helps reduce the risk of incomplete excision or recurrence.

6. Post-Surgical Evaluation and Treatment in Appendiceal Neuroendocrine Neoplasms (ANENs)

After surgical intervention for Appendiceal Neuroendocrine Neoplasms (ANENs), it is essential to perform a comprehensive post-surgical evaluation. This evaluation is critical in identifying patients who may require additional therapy and making informed decisions regarding post-surgical treatments. Several factors influence these decisions, with histological grading playing a pivotal role.

7. Identifying Patients Requiring Additional Therapy

7.1. Histological Grade

The histological grade of ANENs is a key determinant in post-surgical treatment decisions. ANENs are classified into three grades:

- Grade 1 (Well-differentiated): These tumors are typically slow-growing and less aggressive. They may require less aggressive post-surgical treatment, if any.
- Grade 2 (Intermediate-grade): Intermediate-grade ANENs exhibit moderate aggressiveness and may benefit from additional therapies to prevent recurrence.
- Grade 3 (Poorly differentiated): Poorly differentiated ANENs are highly aggressive and typically require aggressive post-surgical treatment, often involving chemotherapy.

7.2. Tumour Size and Invasion

The size of the primary tumor and the extent of invasion into surrounding tissues are critical factors. Larger tumors or those with extensive invasion are associated with a higher risk of recurrence and may require additional therapy. Small tumors, often less than 1 centimeter in diameter, are typically associated with a lower risk of aggressive behavior. They are more likely to be well-differentiated (Grade 1) and may require minimal or no post-surgical treatment beyond complete resection. Intermediate-sized Tumors ranging from 1 to 2 centimeters or slightly larger are considered intermediate-sized. The size of these tumors may influence the decision to perform additional treatments following surgery. While some intermediate-sized tumors may still be well-differentiated and low-grade, others may exhibit features suggesting a higher risk

of recurrence. Large Tumors larger than 2 centimeters are generally associated with an increased risk of aggressive behavior, including invasion of surrounding tissues and metastasis. Large ANENs are more likely to be intermediate-grade (Grade 2) or poorly differentiated (Grade 3). These patients often require more aggressive post-surgical treatments to reduce the risk of recurrence and metastasis.

7.3. Lymph Node Involvement

The presence of lymph node metastasis indicates a higher risk of disease recurrence. Patients with lymph node involvement may benefit from adjuvant therapies. Lymph node involvement is a critical factor in the staging and management of appendiceal neuroendocrine neoplasms (ANENs). The presence or absence of lymph node metastases has a significant impact on treatment decisions and prognosis. Lymph node involvement is an important component of cancer staging. In ANENs, the staging system used is often based on the TNM (Tumor, Nodes, Metastasis) classification system. The extent of lymph node involvement, such as the number of affected lymph nodes and their location, helps determine the stage of the disease. Stages can range from localized disease (limited to the appendix) to regional lymph node involvement and distant metastasis. The presence of lymph node metastases may influence treatment decisions. For patients with localized ANENs (Stage I), where there is no evidence of lymph node involvement or distant metastasis, surgical resection, such as an appendectomy, may be curative. However, in cases of regional lymph node involvement (Stage II and III) or distant metastasis (Stage IV), more aggressive treatments, such as additional surgery, systemic therapies (chemotherapy, targeted therapy, or PRRT), or other locoregional treatments, may be considered. Lymph node involvement is a prognostic factor. Generally, the presence of lymph node metastases is associated with a higher risk of disease recurrence and poorer survival outcomes. The extent of lymph node involvement, including the number of affected lymph nodes and their size, can further refine prognosis. In some cases, surgeons may perform lymph node dissection (removal of affected lymph nodes) as part of the surgical procedure. The decision to perform lymph node dissection depends on the extent of disease and the surgeon’s judgment. Lymph node dissection aims to remove cancerous lymph nodes to reduce the risk of local recurrence. Accurate pathological examination of lymph nodes is crucial. It helps confirm the presence of metastatic disease and provides information about the extent of lymph node involvement.

Pathologists examine lymph nodes under a microscope to identify cancer cells. Patients with lymph node involvement often require more rigorous follow-up to monitor for disease recurrence or progression. Imaging studies and other tests may be performed at regular intervals to assess the status of lymph nodes and the disease. It's important to emphasize that the management of ANENs, including the approach to lymph node involvement, should be individualized based on factors such as the tumor's grade, size, location, and overall health of the patient. Multidisciplinary discussions involving surgeons, oncologists, pathologists, and other specialists are often essential to develop the most appropriate treatment plan for each patient.

7.4. Extent of Surgery

The type of surgery performed, whether it's a simple appendectomy, right hemicolectomy, or cytoreductive surgery for metastases, influences the risk of recurrence and the need for additional therapy. The extent of surgery for appendiceal neuroendocrine neoplasms (ANENs) depends on several factors, including the size and location of the tumor, the presence of lymph node involvement, and the tumor grade. (20)

7.4.1. Tumor Size and Location

Small, localized ANENs can often be managed with a less extensive surgical procedure, such as an appendectomy. An appendectomy involves the removal of the appendix and is typically curative for early-stage, well-differentiated tumors that have not spread beyond the appendix. This approach is suitable for tumors that are confined to the appendix and do not involve the base of the appendix. (16, 17)

7.4.2. Tumor Grade

The grade of the tumor is a critical factor in surgical decision-making. Well-differentiated, low-grade ANENs are associated with a more favorable prognosis, and localized disease may be treated with appendectomy alone. In contrast, high-grade ANENs, which are more aggressive, often require more extensive surgery.

7.4.3. Lymph Node Involvement

The presence of lymph node metastases may necessitate more extensive surgery. If there is evidence of regional lymph node involvement, a right

hemicolectomy may be recommended. A right hemicolectomy involves the removal of the cecum, ascending colon, and a portion of the transverse colon, along with the lymph nodes in that area. This procedure aims to remove both the primary tumor and affected lymph nodes. (21,22)

7.4.4. Multifocal or Disseminated Disease

In cases where ANENs are multifocal (occurring in multiple locations within the appendix) or have disseminated (spread) beyond the appendix to nearby organs or distant sites, a more extensive surgical approach may be required. This could involve removal of affected portions of other organs or tissues, depending on the extent of spread.

7.4.5. Margins and Microscopic Resection

Achieving clear surgical margins and ensuring complete microscopic resection of the tumor are essential goals of surgery. The surgeon will aim to remove the tumor with adequate healthy tissue margins to minimize the risk of local recurrence.

7.4.6. Patient Health and Individual Factors

The overall health and individual circumstances of the patient are also considered when determining the extent of surgery. For some patients, particularly those with significant comorbidities, a less aggressive surgical approach may be chosen.

7.4.7. Pathological Examination

The final extent of surgery may also depend on the results of pathological examination. Detailed examination of the surgical specimen by a pathologist can provide information about the tumor's size, grade, margin status, and lymph node involvement, which can guide further treatment decisions. In summary, the extent of surgery for ANENs is highly individualized and depends on multiple factors. Small, well-differentiated tumors confined to the appendix may be managed with appendectomy alone. In contrast, larger tumors, high-grade tumors, or those with lymph node involvement often require more extensive procedures, such as right hemicolectomy or additional organ resections. Multidisciplinary discussions involving surgeons, oncologists, and pathologists are crucial in making informed decisions about the extent of surgery and subsequent treatment strategies. (23)

8. The management of metastatic appendiceal neuroendocrine neoplasms (ANENs)

Involves a variety of therapeutic options that aim to control the disease, alleviate symptoms, and improve the patient's quality of life. The choice of therapy depends on several factors, including tumor grade, the site and extent of metastatic disease, and individual patient characteristics. Here are the therapeutic options commonly considered for metastatic ANENs:

8.1. Surgery

Surgical interventions may still play a role in the management of metastatic ANENs, especially if there are localized metastases that can be surgically removed or debulked. This approach is more common in patients with low to intermediate-grade tumors who are symptomatic due to liver metastases. Surgical cytoreduction can help alleviate symptoms and potentially extend survival.

8.2. Liver Directed Therapy

Liver metastases are common in ANENs, and various liver-directed therapies can be considered when surgical resection is not feasible. These therapies include:

8.2.1. Hepatic Artery Embolization

This procedure involves blocking the hepatic artery to reduce blood flow to the liver tumors. It is used to shrink liver metastases and control symptoms. Hepatic artery embolization is a medical procedure used in the treatment of certain liver conditions, including metastatic neuroendocrine tumors (NETs) like appendiceal neuroendocrine neoplasms (ANENs). This procedure is primarily employed when surgical removal or resection of liver metastases is not feasible or as a palliative measure to alleviate symptoms and reduce tumor burden. Hepatic artery embolization is a minimally invasive procedure performed by an interventional radiologist. It involves blocking or reducing the blood supply to liver tumors by injecting embolic agents into the hepatic artery, which is the main blood vessel supplying the liver. The primary goal of hepatic artery embolization is to limit or reduce the blood flow to liver metastases, thereby causing tumor shrinkage or necrosis. This procedure can help alleviate symptoms associated with liver metastases, such as pain, discomfort, and hormonal symptoms (e.g., flushing and diarrhea) common in neuroendocrine tumors. Various embolic

agents can be used, including small particles, gels, or coils. These agents block the small blood vessels (capillaries) within or leading to the tumors. By blocking blood flow, embolic agents reduce the supply of oxygen and nutrients to the tumors, leading to tumor cell death. Hepatic artery embolization is typically considered for patients with metastatic liver disease when surgical resection is not a viable option. It is often used in the setting of neuroendocrine tumors, where the liver is a common site of metastasis. The procedure usually begins with local anesthesia at the puncture site, typically in the groin. A catheter is then inserted into a large artery (usually the femoral artery) and advanced to the hepatic artery under imaging guidance (fluoroscopy). Once in place, embolic agents are injected through the catheter into the hepatic artery to block blood flow to the tumors. Imaging is used during the procedure to ensure precise placement of the embolic agents. After hepatic artery embolization, patients may experience some post-procedure discomfort, such as pain or fever, which is usually managed with medications. Patients are monitored in the hospital for a short period following the procedure. Follow-up imaging studies are typically performed to assess the response to embolization and to plan for further treatments if necessary. The effectiveness of hepatic artery embolization can vary from patient to patient. It may lead to tumor shrinkage, symptom relief, and potentially improved quality of life. The duration of response can also vary, and additional treatments may be required over time. Hepatic artery embolization is generally considered safe, but it carries some risks, including damage to normal liver tissue, infection, bleeding, and potential complications related to the catheter insertion site. Patient selection, careful planning, and experienced medical teams are critical to minimizing risks.

8.2.2. Chemoembolization

In this procedure, chemotherapy drugs are delivered directly to the liver tumor site through the hepatic artery, combined with embolization to block blood flow. It can help control tumor growth and relieve symptoms. Transarterial chemoembolization (TACE) is a medical procedure used in the treatment of certain liver conditions, including metastatic neuroendocrine tumors (NETs) like appendiceal neuroendocrine neoplasms (ANENs) when the tumors have spread to the liver. This procedure combines the delivery of chemotherapy drugs directly to the tumor site with the embolization of blood vessels to restrict blood flow. Chemoembolization aims to treat liver metastases by delivering chemotherapy drugs directly into the hepatic artery,

which supplies blood to liver tumors. The procedure combines the effects of localized chemotherapy with the physical blockage (embolization) of the blood vessels feeding the tumor. Chemoembolization is typically performed by an interventional radiologist. The procedure begins with the insertion of a catheter into an artery, often in the groin area, which is then threaded through the blood vessels and into the hepatic artery under imaging guidance. Once the catheter is in place, chemotherapy drugs, often mixed with a contrast agent, are injected directly into the hepatic artery, allowing for high local concentrations of the drugs within the liver. Following drug infusion, the physician uses embolic agents (such as small beads or gels) to block or restrict blood flow in the arteries feeding the tumor, causing ischemia (lack of blood supply) and, ultimately, tumor cell death. Chemoembolization can be an effective treatment for liver metastases, particularly in patients where surgical resection is not possible. The localized delivery of chemotherapy allows for higher drug concentrations at the tumor site while minimizing systemic side effects. The embolization step further enhances treatment by cutting off the blood supply to the tumor. Chemoembolization is generally considered for patients with liver-dominant metastatic disease, including neuroendocrine tumors like ANENs. Candidates for this procedure are often evaluated based on tumor size, location, and liver function. After chemoembolization, patients may experience some post-procedure discomfort, such as abdominal pain or fever. Patients are usually monitored in the hospital for a brief period following the procedure. Follow-up imaging studies, such as CT scans or MRI, are performed to assess the response to chemoembolization and determine the need for additional treatments. Chemoembolization is generally safe, but it carries certain risks, including liver damage, infection, bleeding, and potential complications related to catheter insertion. Patients should be carefully selected, and the procedure should be performed by experienced medical teams to minimize risks.

8.2.3. Radioembolizatoin (PRRT)

Radioembolization involves the use of radiolabeled microspheres (such as Lutetium-177) to deliver targeted radiation to liver metastases. This therapy can be effective in reducing tumor burden and extending survival. Radioembolization, also known as selective internal radiation therapy (SIRT) or transarterial radioembolization (TARE), is a medical procedure used in the treatment of liver tumors, including metastatic neuroendocrine tumors (NETs) like appendiceal neuroendocrine neoplasms (ANENs) when they have spread to

the liver. This technique delivers radiation directly to liver tumors while sparing healthy liver tissue. Radioembolization is performed with the aim of treating liver metastases by delivering localized radiation therapy to the tumor site. It is especially useful when the disease is confined primarily to the liver, and surgical resection is not feasible or as a palliative measure to control tumor growth and symptoms. Radioembolization is usually performed by an interventional radiologist. The procedure starts with the placement of a catheter into an artery, typically in the groin area. This catheter is then threaded through blood vessels until it reaches the hepatic artery, which supplies blood to the liver. Tiny radioactive beads, known as microspheres or spheres, are introduced through the catheter directly into the hepatic artery. These beads contain a radioactive substance, such as yttrium-90 (Y-90). The microspheres become lodged in the small blood vessels within or near the tumor, where they emit radiation over time, effectively irradiating the tumor from the inside. Healthy liver tissue is relatively resistant to radiation, so the procedure minimizes damage to normal liver cells. Radioembolization is effective in treating liver metastases, including those from NETs like ANENs. It provides localized radiation, which can help shrink tumors and relieve symptoms while minimizing radiation exposure to surrounding healthy tissue. Patients considered for radioembolization typically have liver-dominant disease. Candidates are evaluated based on factors such as the size and location of liver tumors, liver function, and overall health. Following radioembolization, patients may experience some post-procedure discomfort, fatigue, or mild flu-like symptoms. Most patients can return home on the same day or the day after the procedure. Regular follow-up imaging studies, such as CT scans or SPECT scans, are performed to monitor the response to treatment and assess the need for further interventions. Radioembolization is generally considered safe, but it carries certain risks, including liver damage, radiation-related side effects, and potential complications related to catheter placement. Patients should be carefully selected, and the procedure should be performed by experienced medical teams.

8.3. Ablative Techniques

Ablative techniques are medical procedures that use various methods to destroy tumors or abnormal tissue without the need for surgery. These techniques can be employed in the treatment of liver metastases from appendiceal neuroendocrine neoplasms (ANENs) or other tumors. Here are some common ablative techniques used for liver tumors:

8.3.1. Radiofrequency Ablation (RFA)

RFA uses high-frequency electrical currents to heat and destroy cancerous tissue. A specialized needle electrode is inserted directly into the tumor through the skin or during surgery. The electrode generates heat, which causes coagulative necrosis, effectively killing the tumor cells. RFA is suitable for small liver tumors (usually less than 5 cm in diameter).

- **Needle Electrode Placement**: During an RFA procedure, a specialized needle electrode is inserted directly into the tumor. This can be done using image guidance, such as ultrasound, CT scans, or MRI, to ensure precise placement. Once the electrode is in position within the tumor, an alternating electrical current is passed through it. This generates heat, causing coagulative necrosis, which effectively kills the tumor cells. The procedure is typically performed with real-time monitoring using imaging techniques to ensure that the entire tumor is adequately treated while avoiding damage to surrounding healthy tissue. RFA is most effective for small to medium-sized tumors, usually those less than 5 centimeters in diameter. It's particularly useful for tumors located near the surface of the liver or in areas where surgical resection may be challenging. Patients who are not good candidates for surgery due to underlying health issues may benefit from RFA. RFA can also be used to treat multiple tumors in the liver simultaneously.

- **Advantages of RFA** are as follows: RFA is less invasive than traditional surgery, resulting in smaller incisions, reduced pain, and shorter recovery times. In many cases, RFA can be performed as an outpatient procedure, meaning patients can go home the same day. RFA precisely targets the tumor, minimizing damage to healthy liver tissue. RFA can provide relief from symptoms associated with liver tumors, such as pain or discomfort.

- **Limitation:** RFA may not be suitable for large tumors, as it may be less effective in completely destroying them. Tumors located near major blood vessels or bile ducts may be challenging to treat with RFA. There is a risk of tumor recurrence after RFA, and patients may require additional treatments or monitoring.

8.3.2. Microwave Ablation (MWA)

MWA is similar to RFA but uses microwaves instead of electrical currents to create heat. It has the advantage of faster and larger-volume tissue heating, making it suitable for larger tumors. Microwave Ablation (MWA) is a medical

procedure used for the treatment of tumors, including liver tumors such as metastatic lesions from cancers like appendiceal neuroendocrine neoplasms (ANENs). Similar to Radiofrequency Ablation (RFA), MWA is a minimally invasive technique designed to destroy cancerous or abnormal tissue using thermal energy. However, MWA uses microwaves instead of radiofrequency waves to achieve this. During an MWA procedure, a thin, needle-like probe with a microwave-emitting antenna at its tip is inserted directly into the tumor. This is usually done with the guidance of imaging techniques like ultrasound, CT scans, or MRI to ensure precise placement. Once the probe is properly positioned within the tumor, microwave energy is emitted from the antenna. This energy rapidly oscillates water molecules within the tissue, generating heat. The heat produced by the microwave energy causes coagulative necrosis, which essentially "cooks" the tumor tissue. This process destroys the tumor cells, effectively treating the cancerous lesion. The procedure is performed under real-time imaging guidance to monitor the progress and ensure that the entire tumor is adequately treated while sparing healthy surrounding tissue. MWA is most effective for small to medium-sized tumors, typically those less than 5 centimeters in diameter. It is particularly suitable for tumors located near the surface of the liver or in areas where surgical resection may be challenging. Patients who are not suitable candidates for surgery due to underlying health conditions or those looking for a minimally invasive approach may benefit from MWA. MWA can also be used to treat multiple tumors in the liver simultaneously. MWA is less invasive than traditional surgery, resulting in smaller incisions, less pain, and shorter recovery times. In many cases, MWA can be performed as an outpatient procedure, allowing patients to return home on the same day. MWA precisely targets the tumor, minimizing damage to healthy liver tissue. MWA can provide relief from symptoms associated with liver tumors, such as pain or discomfort. Tumor Siz MWA may not be suitable for large tumors, as it may be less effective in completely destroying them. Tumors located near major blood vessels or bile ducts may be challenging to treat with MWA. There is a risk of tumor recurrence after MWA, and patients may require additional treatments or monitoring.

8.3.3. Cryoablation

Cryoablation involves freezing and thawing tumor tissue to destroy it. A probe containing a cryogenic gas (liquid nitrogen or argon gas) is inserted into the tumor. The freezing process forms ice crystals within the tumor cells, causing them to rupture. Cryoablation, also known as cryotherapy or cryosurgery, is

a medical procedure used for the treatment of various medical conditions, including liver tumors such as metastatic lesions from cancers like appendiceal neuroendocrine neoplasms (ANENs). It's a minimally invasive technique that uses extreme cold to freeze and destroy abnormal or cancerous tissue. During a cryoablation procedure, one or more thin, needle-like probes are inserted directly into the tumor. These probes are equipped with freezing gases (usually argon or nitrogen) that create very low temperatures. The freezing gases are circulated through the probes, causing the temperature around the tumor to drop significantly. This rapid freezing leads to the formation of ice crystals within the tumor cells. The freezing process destroys the tumor cells by rupturing their cell membranes and causing cellular damage. Cryoablation works by both freezing and thawing cycles to maximize cell destruction. The procedure is typically performed under real-time imaging guidance, such as ultrasound, CT scans, or MRI, to monitor the progress and ensure that the entire tumor is treated while preserving healthy surrounding tissue. Cryoablation is most effective for small to medium-sized tumors, generally those less than 5 centimeters in diameter. It is suitable for tumors located near the surface of the liver or in areas where surgical resection may be challenging. Patients who are not candidates for surgery due to underlying health conditions or those seeking a minimally invasive approach may benefit from cryoablation. Cryoablation is often used when the disease is limited to the liver or a few specific lesions. Cryoablation is less invasive than traditional surgery, resulting in smaller incisions, less pain, and shorter recovery times. In many cases, cryoablation can be performed as an outpatient procedure, allowing patients to return home on the same day. Cryoablation precisely targets the tumor, minimizing damage to healthy liver tissue. Cryoablation can provide relief from symptoms associated with liver tumors, such as pain or discomfort. Cryoablation may not be suitable for large tumors, as it may be less effective in completely destroying them. Tumors located near major blood vessels or bile ducts may be challenging to treat with cryoablation. There is a risk of tumor recurrence after cryoablation, and patients may require additional treatments or monitoring.

8.4. Medical Therapy:

8.4.1. Somatostatin Analog Therapy

Somatostatin analogs (SSAs) like octreotide and lanreotide are commonly used in patients with well-differentiated NETs, including ANENs. They can help control hormone-related symptoms such as diarrhea and flushing and have

been shown to inhibit tumor growth in some cases. Somatostatin analog therapy is an essential treatment option for neuroendocrine tumors (NETs), including those originating from the appendix (ANENs). Somatostatin is a natural hormone produced in the body that regulates the release of various hormones, including insulin, glucagon, growth hormone, and gastrointestinal hormones. Neuroendocrine tumors often express somatostatin receptors (SSTRs) on their cell surfaces. These receptors can bind to somatostatin. Somatostatin analogs (SSAs) are synthetic compounds that mimic the actions of natural somatostatin. SSAs include medications such as octreotide (Sandostatin) and lanreotide (Somatuline), which have longer half-lives than natural somatostatin, allowing for more sustained effects. These medications bind to SSTRs on NET cells, leading to several beneficial effects: SSAs can control the secretion of hormones that NETs often produce, such as serotonin, insulin, glucagon, and gastrin. This helps manage symptoms like diarrhea, flushing, and hormonal imbalances. SSAs have been shown to slow down tumor growth in some NETs, particularly in well-differentiated and low-grade tumors. By reducing hormone secretion and controlling tumor growth, SSAs can provide relief from NET-related symptoms, improving the patient's quality of life. Clinical trials, such as the PROMID and CLARINET trials, demonstrated the effectiveness of SSAs in controlling tumor growth and extending progression-free survival in patients with metastatic NETs, including those with ANENs. Octreotide and lanreotide are FDA-approved for the treatment of certain NETs, and they are considered a foundational therapy for managing these tumors. Somatostatin analogs are typically administered by subcutaneous injection, although long-acting formulations are available for less frequent dosing. The choice of SSA, dosing schedule, and duration of therapy are determined based on the specific characteristics of the tumor, the patient's symptoms, and response to treatment. SSAs are generally well-tolerated, but some patients may experience side effects, including mild gastrointestinal symptoms, gallstones, and, rarely, changes in blood glucose levels. Monitoring for these side effects and adjusting treatment as needed is essential. Scans such as Ga-68 DOTATATE or Cu-64 PET scans can help determine whether a patient's tumor expresses somatostatin receptors. A positive scan suggests that the tumor is likely to respond to SSA therapy. Treatment with somatostatin analogs is often considered long-term, as they can provide ongoing symptom relief and slow tumor growth. The decision to discontinue treatment is typically made based on individual patient factors and the response to therapy.

8.4.2. Targeted Therapies (mTOR Inhibitors and Anti-Angiogenesis)

Drugs like everolimus (an mTOR inhibitor) and sunitinib (a tyrosine kinase inhibitor) have been approved for the treatment of metastatic NETs. They can slow tumor growth by targeting specific molecular pathways involved in NET development. argeted therapies, including mTOR inhibitors and anti-angiogenesis agents, have become important components of the treatment landscape for neuroendocrine tumors (NETs), including appendiceal neuroendocrine neoplasms (ANENs).

8.4.3. Chemotherapy

Cytotoxic chemotherapy, such as the CAPTEM regimen (capecitabine and temozolomide), may be considered for patients with high-grade ANENs or high tumor burden. Chemotherapy is typically reserved for cases where other treatments have been exhausted. Chemotherapy is a treatment option for neuroendocrine tumors (NETs), including appendiceal neuroendocrine neoplasms (ANENs), particularly in cases with high-grade tumors or extensive metastatic disease.

8.4.3.1. Chemotherapy for High Grade ANENs

High-grade ANENs, especially poorly differentiated neuroendocrine carcinomas (NECs), are more aggressive and may require chemotherapy as a primary treatment modality. Platinum-based chemotherapy, often combined with etoposide, is a common regimen used for high-grade ANENs. Cisplatin or carboplatin in combination with etoposide is similar to the treatment used for small cell lung cancer. The response rate to platinum-based chemotherapy can vary but is often in the range of 30% to 50%. Unfortunately, responses may be of relatively short duration, and overall survival in high-grade NECs is generally poor. Chemotherapy is typically administered in cycles, and the choice of chemotherapy regimen, dosages, and treatment duration will depend on the individual patient's condition and the recommendations of the treating oncologist.

8.4.3.2. Chemotherapy for Metastatic Disease

When ANENs, including high-grade NECs, have metastasized to distant organs or lymph nodes, systemic chemotherapy may be considered as a palliative treatment to control the disease and alleviate symptoms. The decision to initiate

chemotherapy for metastatic ANENs will be influenced by factors such as the extent of metastasis, the patient's overall health, and the tumor's responsiveness to chemotherapy. In addition to platinum-based regimens, other chemotherapy options, such as irinotecan-based regimens (e.g., FOLFIRI) or combinations of chemotherapy agents, may be considered.

8.4.3.3. Second Line and Beyond

Patients with ANENs who progress after first-line chemotherapy may have limited therapeutic options, as treatment response tends to be less robust in subsequent lines of therapy. Clinical trials and experimental therapies may be considered for patients who have exhausted standard treatment options.

9. Clinical Trials

Participation in clinical trials can offer access to innovative treatments and therapies under investigation. Clinical trials are essential for advancing the understanding and treatment of ANENs, especially given their rarity. Clinical trials are research studies conducted with human volunteers to answer specific questions about the safety and effectiveness of new treatments, drugs, or medical procedures. In the context of ANENs, clinical trials aim to find better ways to diagnose, treat, and manage these rare tumors. They can investigate novel therapies, combination treatments, or approaches to improve the quality of life for patients. Clinical trials are typically conducted in several phases:

- **Phase 1:** These trials focus on the safety and dosage of a new treatment. They involve a small number of participants.
- **Phase 2:** These trials assess the treatment's effectiveness and side effects in a larger group of patients.
- **Phase 3:** These are large-scale trials comparing the new treatment to standard treatments or a placebo to determine its overall effectiveness and safety. Patients must provide informed consent before participating in a clinical trial. This means they are fully informed about the trial's purpose, potential risks and benefits, and their rights as participants. In many clinical trials, participants are randomly assigned to different groups, such as the treatment group or a control group (receiving standard treatment or a placebo). This helps ensure unbiased results. Clinical trials have specific endpoints, which are the outcomes used to measure the treatment's success. These endpoints can include survival rates,

tumor response, quality of life, and side effects. Each clinical trial has specific eligibility criteria that participants must meet. These criteria may include age, cancer stage, previous treatments, and overall health. Clinical trials are closely monitored to ensure patient safety. Independent committees may review data during the trial to assess the treatment's safety and effectiveness. Clinical trials offer participants the opportunity to access cutting-edge treatments that may not be available through standard care. However, there are no guarantees that the experimental treatment will be more effective than existing therapies. Patients interested in participating in a clinical trial can search for relevant trials through sources like the National Institutes of Health (NIH) database, clinical trial registries, or by consulting with their oncologist. While clinical trials can offer potential benefits, they also come with risks, including unknown side effects and the possibility of receiving a placebo. Patients should discuss these aspects with their healthcare team. By participating in clinical trials, patients contribute to advancing medical knowledge and improving treatments for ANENs. Even if a specific trial doesn't benefit the individual patient, the data collected can help future patients.

10. Symptom Management

Regardless of the specific treatment chosen, symptom management and supportive care are crucial aspects of managing metastatic ANENs. This includes addressing symptoms like diarrhea, pain, hormonal imbalances, and nutritional issues. Symptom management is a crucial aspect of caring for patients with appendiceal neuroendocrine neoplasms (ANENs). These tumors can cause a range of symptoms due to hormone secretion or the physical impact of the tumor itself. Managing these symptoms effectively is essential to improve the patient's quality of life.

10.1. Carcinoid Syndrome Symptoms

Flushing, characterized by redness and warmth of the face and neck, is a hallmark symptom of carcinoid syndrome. It can be triggered by various factors, including stress, certain foods, or alcohol. Management strategies include avoiding triggers, using antihistamines, and somatostatin analog therapy (e.g., octreotide) to reduce hormone secretion. *Diarrhea* is another common symptom of carcinoid syndrome. Dietary modifications, such as reducing fiber and avoiding trigger foods, can help. Medications like loperamide (Imodium)

may be prescribed for diarrhea control. Somatostatin analogs can also reduce diarrhea in some patients. *Abdominal pain* can result from tumor growth or tumor-related complications. Pain management may involve over-the-counter pain relievers, prescription medications, or procedures like nerve blocks. In some cases, surgical interventions may be necessary to relieve pain.

10.2. Surgical Symptoms

After surgery, patients may experience *pain* at the surgical site. Pain management typically includes prescribed pain medications, which may be adjusted based on the patient's pain level. *Proper care of the surgical incision* is essential to prevent infection and promote healing. Patients should keep the incision clean and dry and follow their healthcare provider's instructions for wound care.

10.3. Nutritional Support

Malabsorption can occur in patients with ANENs, leading to weight loss and nutrient deficiencies. Nutritional support, such as working with a registered dietitian, may be necessary to address specific dietary needs, including supplements or specialized diets. Depending on the extent of malabsorption, patients may require nutrient replacements, such as vitamin B12 injections or calcium and vitamin D supplements.

10.4. Hormone-Related Symptoms

Some patients may experience high blood sugar levels due to hormone secretion. Managing hyperglycemia may involve diabetes medications or insulin therapy.

10.5. Psychological Support

Living with a chronic illness like ANENs can be emotionally challenging. Patients may benefit from psychological support, such as counseling or support groups, to cope with anxiety and depression.

10.6. Multidisciplinary Care

In cases where ANENs are advanced and not curable, palliative care specialists can help manage symptoms and improve the patient's overall quality of life.

10.8. Regular Follow-Up

Regular follow-up appointments with oncologists and other specialists are essential to monitor the disease's progression, manage symptoms, and adjust treatment plans as needed.

10.9. Medication Adherence

For patients prescribed somatostatin analogs (e.g., octreotide or lanreotide), adherence to the treatment plan is crucial to control symptoms effectively.

11. Multidisciplinary Care

ANENs are best managed through a multidisciplinary approach involving medical oncologists, surgical oncologists, radiologists, and other specialists. A tailored treatment plan should be developed based on the patient's unique circumstances.

12. Patient Education and Support

Providing patients with information about their condition, treatment options, and support resources is essential. Patients should be actively involved in decisions about their care.

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CHAPTER III

ABDOMINAL WALL HERNIAS

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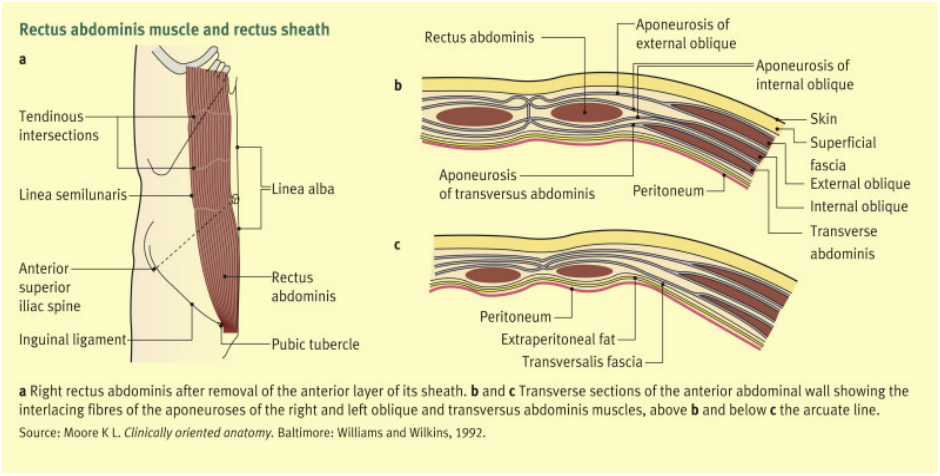
1. Introduction

Abdominal wall hernias are quite common diseases amongst population in all countries. Every general surgeon encounters very high numbers of these hernias in his or her daily practice. Consequently repair surgeries of abdominal wall hernias are very commonly applied surgical treatments. Most of these hernias are inguinal and they are mostly seen in males. More than one million abdominal wall hernia repair operations are performed in the United States annually. (1-3) By the way getting used to these surgeries and enhancing the knowledge about abdominal wall anatomy, pathophysiology of hernias and their treatment techniques are essential in general surgery. In this chapter mainly types and repair techniques of abdominal wall hernias will be emphasised.

2. Anatomy of Abdominal Wall and Types of Hernias

2.1. Anatomy

Abdominal wall consists of skin, fat, muscles, fascias, aponeurosis and peritoneum. Some regions of this wall are weaker than overall. So when there is a problem with general tissue quality or personal behaviours, hernias are tend to emerge rather from these regions. General and principal anatomy and abdominal wall layers are shown in figure (Figure 1).



a Right rectus abdominis after removal of the anterior layer of its sheath. **b** and **c** Transverse sections of the anterior abdominal wall showing the interlacing fibres of the aponeuroses of the right and left oblique and transversus abdominis muscles, above **b** and below **c** the arcuate line.
Source: Moore K L. *Clinically oriented anatomy.* Baltimore: Williams and Wilkins, 1992.

Figure 1: Briefly abdominal wall and its layers
(Clinically Oriented Anatomy. Baltimore: Williams and Wilkins, 1992)

2.2. Types of abdominal wall hernias

There are several abdominal wall hernia typses according to their originating region (Figure 2). Generally all of these hernias can be divided into two parts: Groin Hernias and Ventral Hernias. Approximately 75% of abdominal wall hernias are groin hernias. Groin hernias consists of inguinal and femoral hernias. Direct inguinal hernias originate from Hasselbach's Triangle while indirect inguinal hernias travel through inguinal canal. Femoral hernia originates from femoral ring as its name signifies.

From one of ventral hernias is lumbar hernia. It is a very rare hernia type. (4) Lumbar hernia may occur in two areas of the posterolateral abdominal wall. Frequent one is superior lumbar triangle of Grynfeltt, and sparse one is inferior lumbar triangle of Petit. In large hernias all of the lumbar region may be affected. (5,6)

Spigelian Hernia takes its name from 'der Spiegel', mirror in German Language. Because its originates from the linea semilunaris and this line is likened to an oval mirror.

Umblical hernias are also common ones. They originate from an umblical fascial defect mostly congenital. When hernias protrude through linea alba around umblicus, they are called periumblical hernias. If this occurs from the very upper parts of linea alba, they are called epigastric hernias.

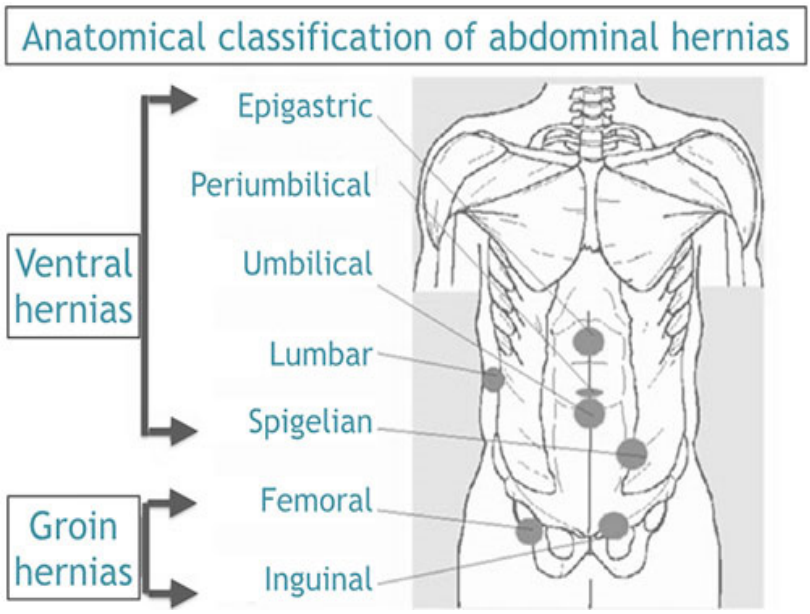


Figure 2: Types of Abdominal Wall Hernias

Some rather rare conditions are named differently from those anatomical classification. A Richter hernia is a clinical condition that the only antimesenteric side of the bowel is herniated through defect. No obstructive findings would be expected even if an incarcereted part was present. This may end up with unexpected perforation after a smooth reduction. Every abdominal wall hernia may carry Richter properties.

A Littre Hernia is an abdominal wall hernia with a Meckel Diverticule inside. Also Amyand Hernia is a groin hernia with Appendix Vermiformis inside the sac. A Maydl Hernia is the condition if a 'W' shaped bowel is inside the sac. The bowel part between this segments is inside the abdomen and it is a double closed border, blind loop.

An incisional hernia is an unwanted iatrogenic result that occurs in 2-10% of all abdominal operations secondary to breakdown of the fascial closure.

3. Signs and Symptoms

Swelling and little pain sensation at the hernia site but no true pain or tenderness upon examination, inflation of swelling with increased intra-abdominal pressure are main signs of asymptomatic hernias. Adding on of pain,

enlargement of swelling, unability of manipulating of hernia sac, nausea and vomiting are main symptoms of incarceration. Strangulation of hernia contents may add on symptoms like systemic toxicity because of ischemic bowel, continuing of pain after reduction and acute abdomen findings.

4. Diagnosis

Main tools for diagnosis are history taking and physical examination in abdominal wall hernias. History and examination would reveal where was the hernia, what content was in, how long it was there and whether it could be reducted or not. Also complete blood count, biochemical blood examination and certainly radiographic examinations would be helpful on diagnosis and planning for management.

5. Management

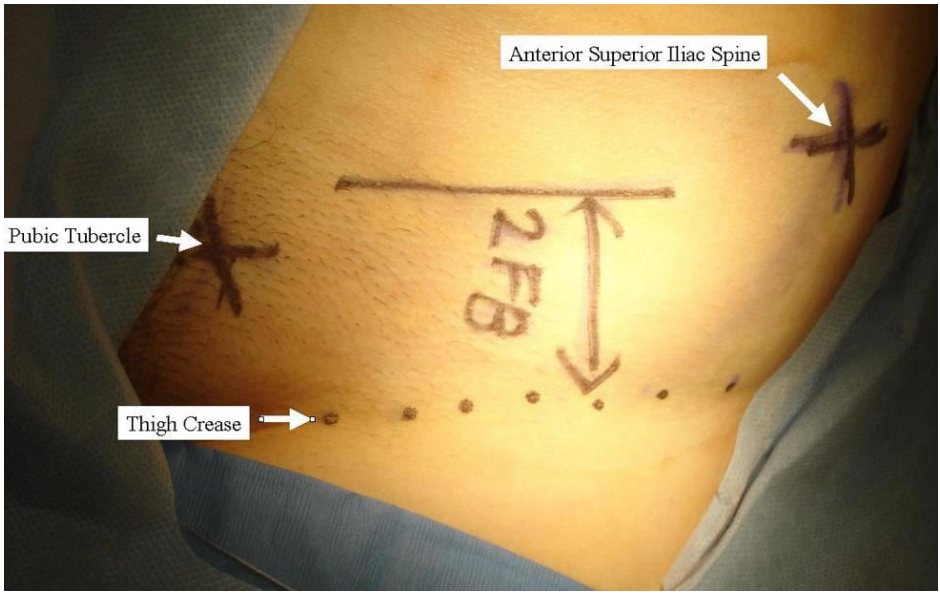
As in all surgically treated diseases it shouldn't be forgotten that all patients are different from each other. Their clinical condition depends on their severity of hernia, comorbidities, duration they had their hernia, jobs, self care, dietary habituals and many other factors. So each patient should be evaluated and treatment should be elected individually. Some patients may be treated topically like wearing corsets, some may be operated. Also surgical techniques should be elected individually for each patient.

In this chapter mainly surgical treatment modalities will be mentioned.

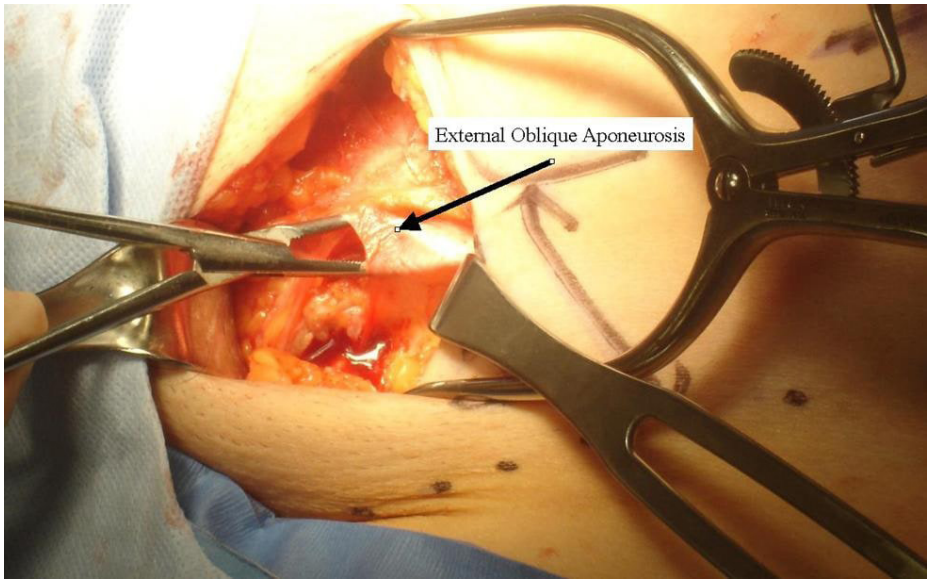
5.1 Surgical treatment of Different Types of Hernias

5.1.1 Inguinal Hernia

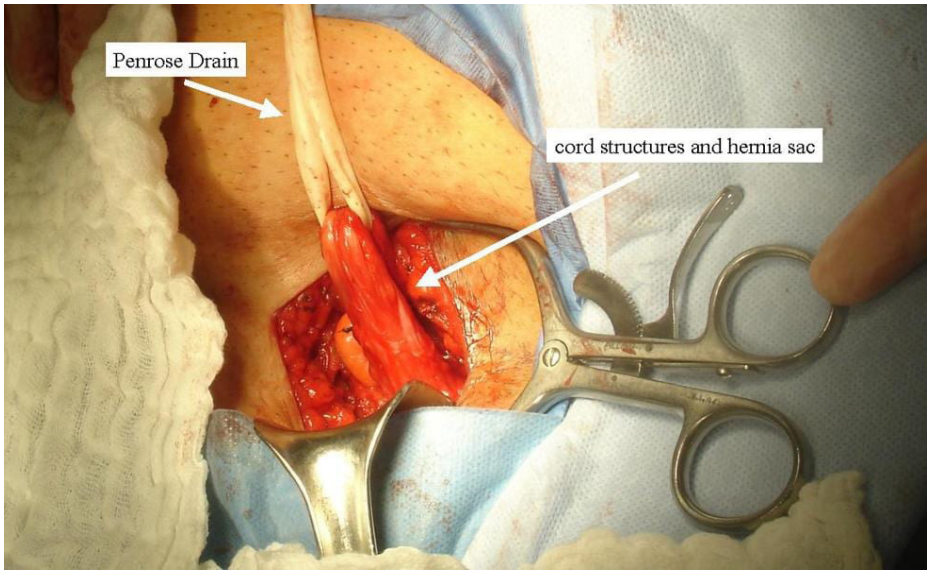
Inguinal hernias are quite common hernias as mentioned in the introduction part. Surgical approaches are the main treatment methods. The Lichtenstein tension-free mesh repair method is an example of hernioplasty and is currently one of the most popular open inguinal hernia repair techniques. This procedure will be tried to be represented with pictures and explanations below. (7)(pictures 1-9)



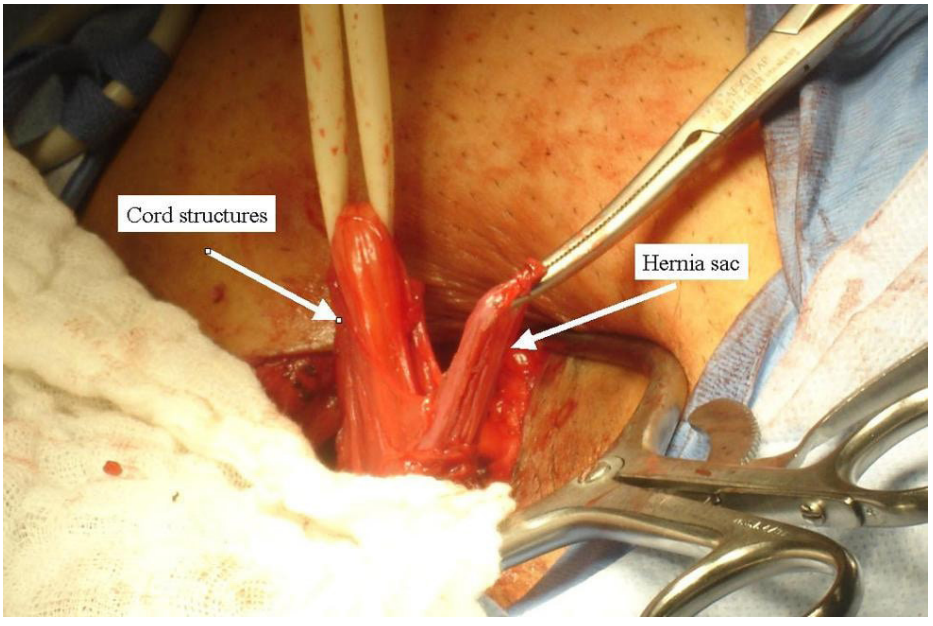
Picture 1: Opening incision for inguinal hernia repair. By this opening all the skin and subcutaneus fat should be passed. (Vinay K Kapoor, MBBS, MS, FRCSEd, FICS, FAMS Professor of HPB Surgery, Mahatma Gandhi Medical College and Hospital (MGMCH), Jaipur, India)



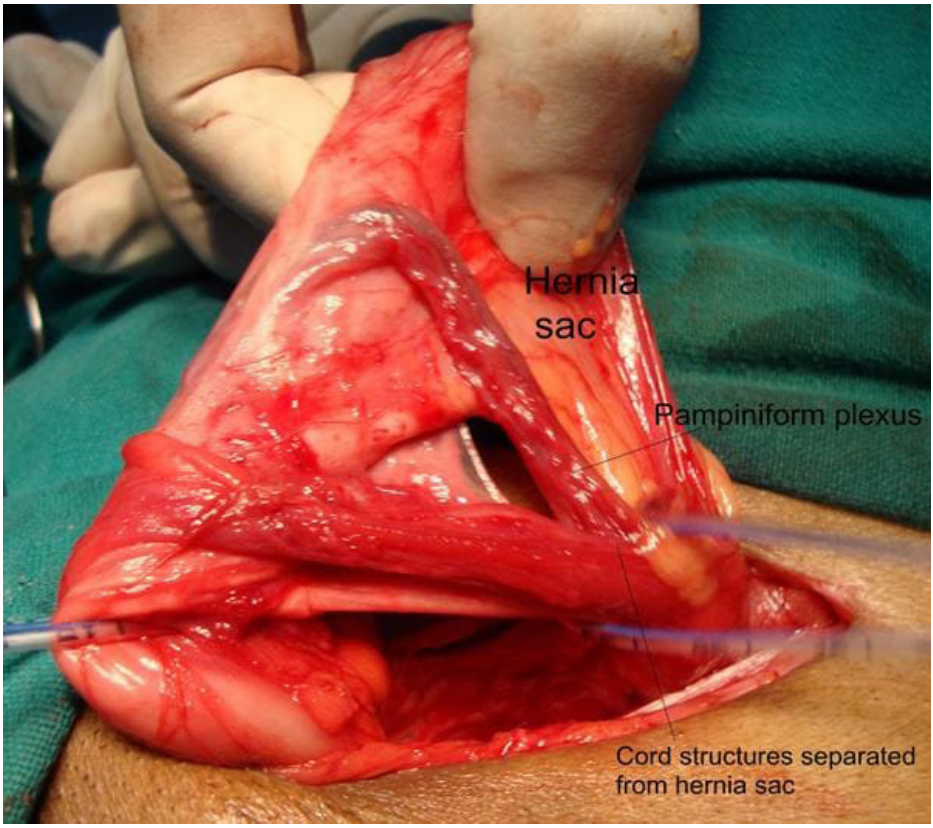
Picture 2: External oblique aponeurosis should be cut opened.



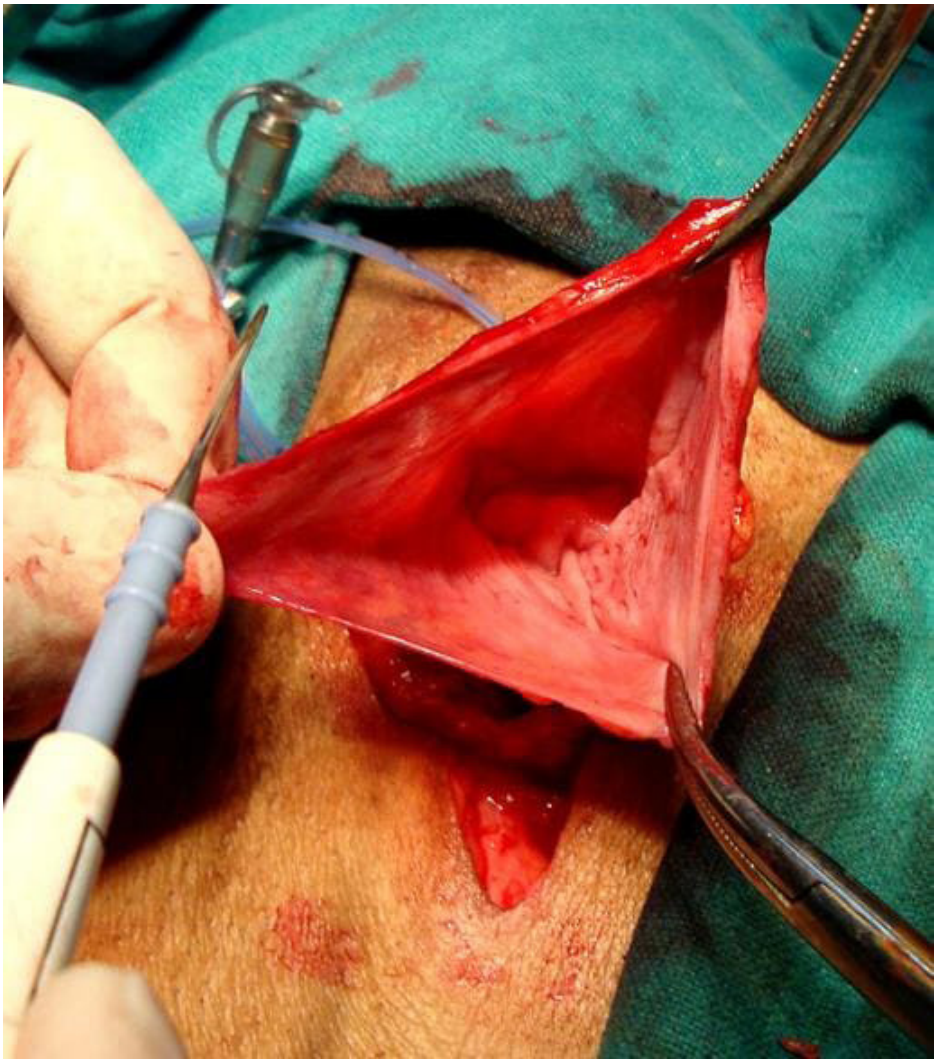
Picture 3: Cord structures and hernia sac should be seperated from surrounding tissue and stringed up with a penrose drain.



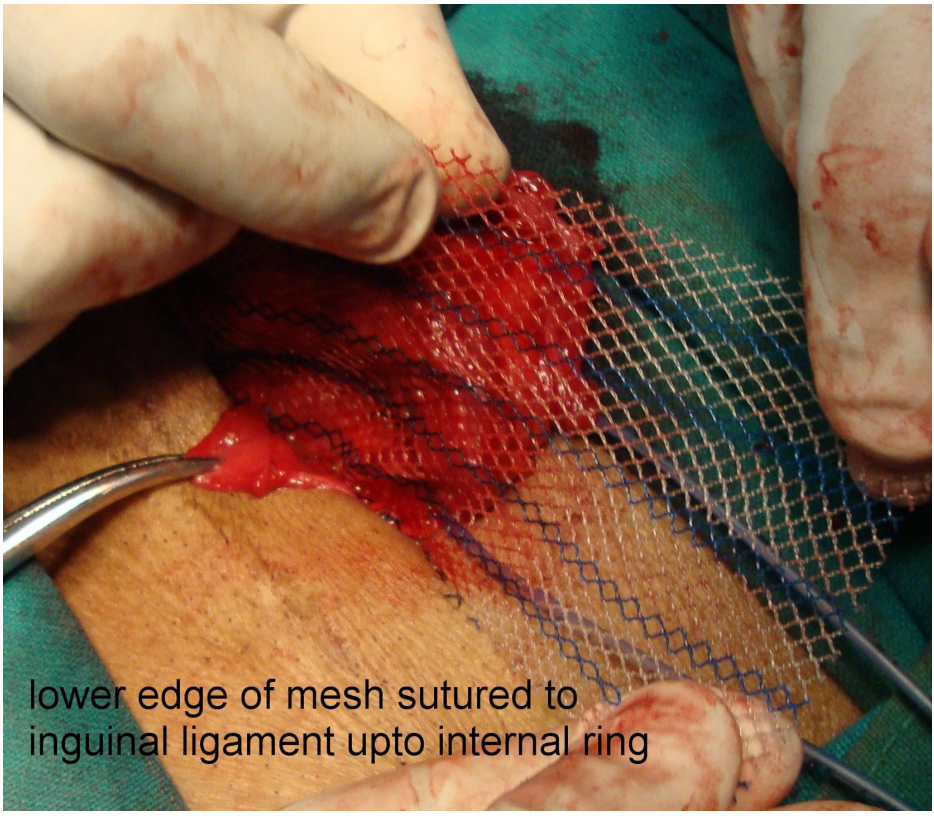
Picture 4: Hernia sac should be seperated from cord structures.



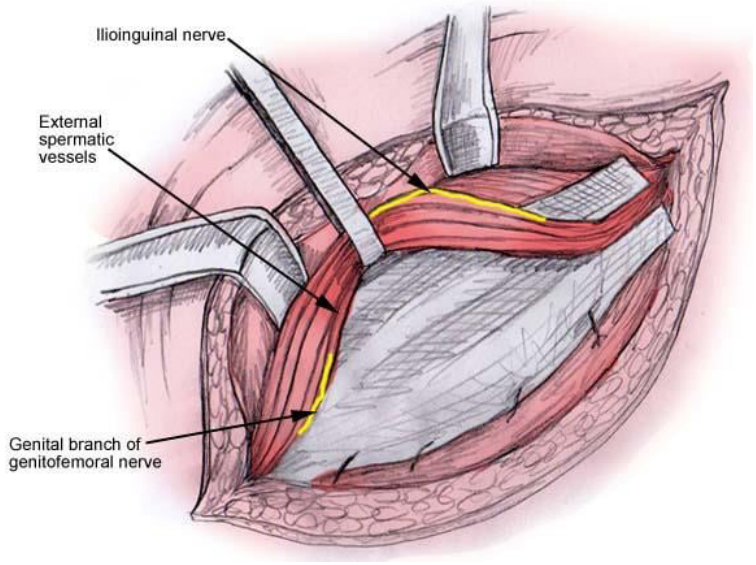
Picture 5: Sometimes there can be a considerably big hernia sac. It could suppress neighboring structures. Seperation should be made elegantly to avoid tissue damage.



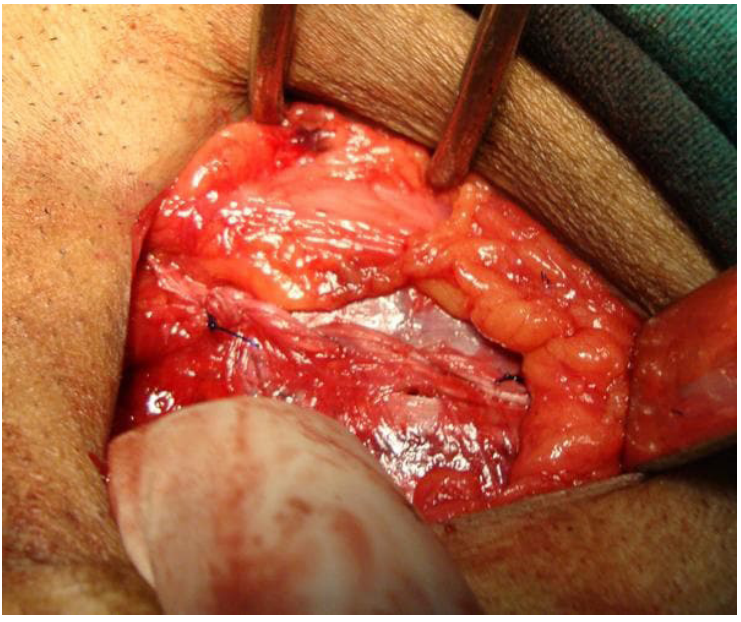
Picture 6: This big hernia sacs are sometimes needed to be hung, cut opened, ensured for contents, resected and stump sutured. The stump then can be repelled to abdomen through the canal it came from. After that mostly a narrowing suture should be made to external inguinal ring to remove the wideness caused by the sac and prevent re-herniation.



Picture 7: After obliteration of the hernia sac, a polypropilen mesh is used to reinforce transverse fascia. It's tip point should be placed on pubic tubercle. First suture should pass through lacunar ligament and after that it should continue till the mesh linage passes external ring line. Sutures should pass from end parts of transvers fascia and few end fibers of inguinal ligament for strength. Extreme caution is necessary to avoid femoral vessels and nerve injury with suturation.



Picture 8: Ilioinguinal, iliohypogastric and genitofemoral nerves should be spared from sutures.



Picture 9: Transverse fascia should be sutured and closed anatomically. This doesn't contribute to hernia repair but it prevents sticking between subcutaneous tissues and mesh, hindering discomfort during mobility. Subcutaneous fat and skin are sutured and closed for finishing the operation.

Other approaches to open inguinal hernia repair are as follows:

Plug-and-patch repair: This technique includes a polypropylene plug shaped mesh, which can be placed into the internal ring after indirect hernia sec reduction.

McVay repair: In this approach, the conjoined tendon is sutured to the Cooper ligament with individual, non-continuous, nonabsorbable sutures.

Bassini repair: This approach involves suturing the transversalis fascia and the conjoined tendon to the inguinal ligament and making a vertical loosening incision in the anterior rectus sheath.

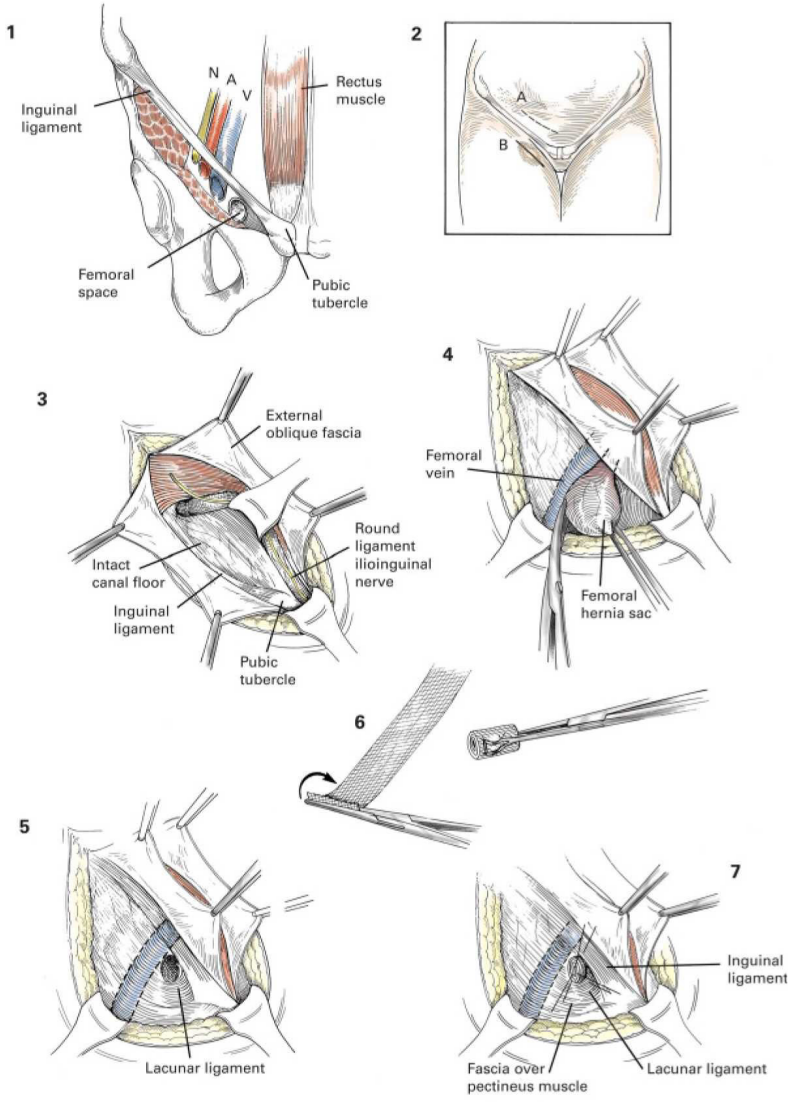
Shouldice repair: This is procedure in which transversalis fascia is incised from the internal ring to the pubic tubercle. Upper and lower flaps are created and then overlapped with two layers of sutures. Conjoined tendon is sutured to the inguinal ligament (in two overlapping layers).

Darn repair: This is a tensionless technique which is performed by placing a continuous suture between the conjoined tendon and the inguinal ligament without closening the two structures.

Also inguinal hernia can be repaired via laparoscopy. Laparospic procedures can be totally extraperitoneal (TEP) or transabdominal Preperitoneal (TAPP). These procedures have been popular since nearly 20 years. They are also safe and acceptable inguinal hernia repair methods. (8,9)

5.1.2 Femoral Hernia

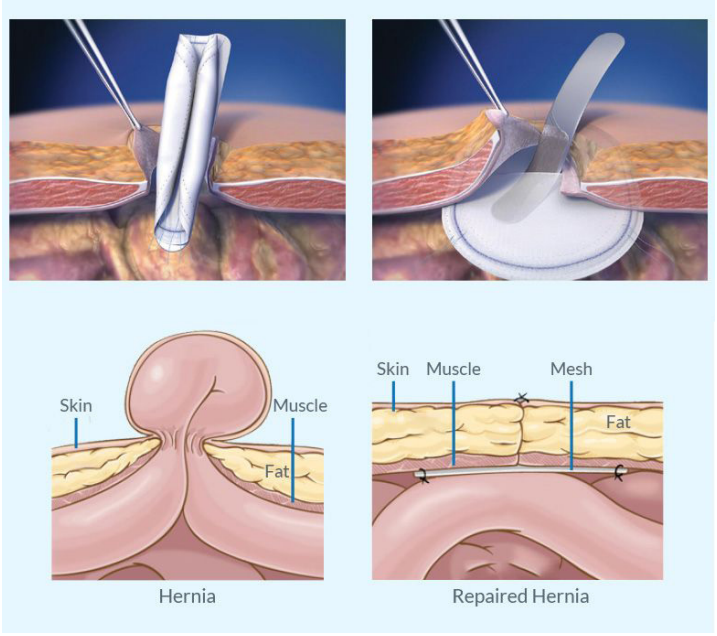
Femoral Hernias consist 5% of all inguinal hernias. They are seen 3-4 times more in females. They come out from narrower Femoral Canal than inguinal canal. They are in neighbourhoood with femoral artery, vein and nerve, therefore their repair is harder and they are more tend to recur.



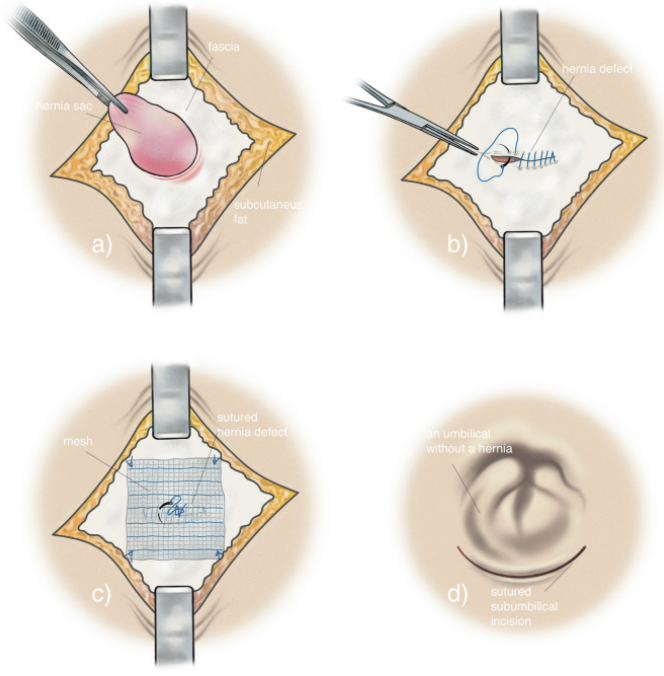
Picture 10: Femoral Hernia repair technique with polypropilene mesh.

5.1.3. Umbilical Hernia

A semicircular or omega incision in the infra or supraumbilical skin crease should be made to reach the umbilical hernia sac. The sac should be seperated from umbilical tract. Upon condition it can be deflected back to abdominal cavity or its excess can be resected after ensuring about contents. After that fascial defect should be sutured and closed. A mesh can be placed preperitoneal (inlay) or on repaired fascia (onlay) depending on width of defect (Pictures 11,12).



Picture 11: Preperitoneal (inlay) mesh technique (Dr. David W. Ford, M.D, FACS



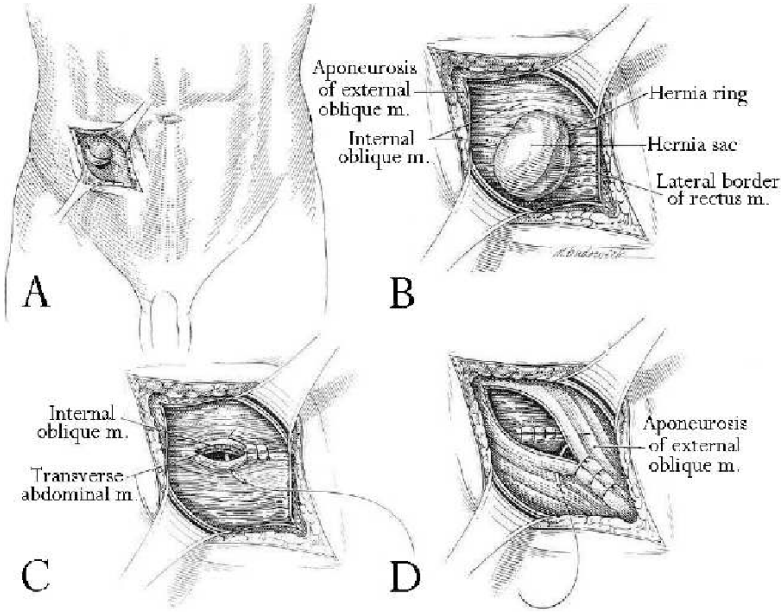
Picture 12: Onlay mesh technique in umbilical hernia repair. (10)

5.1.4. Epigastric Hernia

Epigastric Hernias are also midline hernias like umbilical hernias. They are also repaired via same approach like umbilical hernias. Inlay or onlay mesh can be chosen.

5.1.5 Spiegelian Hernia

Spiegelian hernias are hernias breaking through spiegelian line (linea semilunaris) which is between rectus abdominis medially and transversus abdominis and internal oblique muscles laterally. Hernia sac is found under external oblique aponeurosis. This aponeurosis should be opened, defect should be sutured after sac is deflected back to abdomen. A mesh can be fixed and after that aponeurosis is repaired (Picture 13).

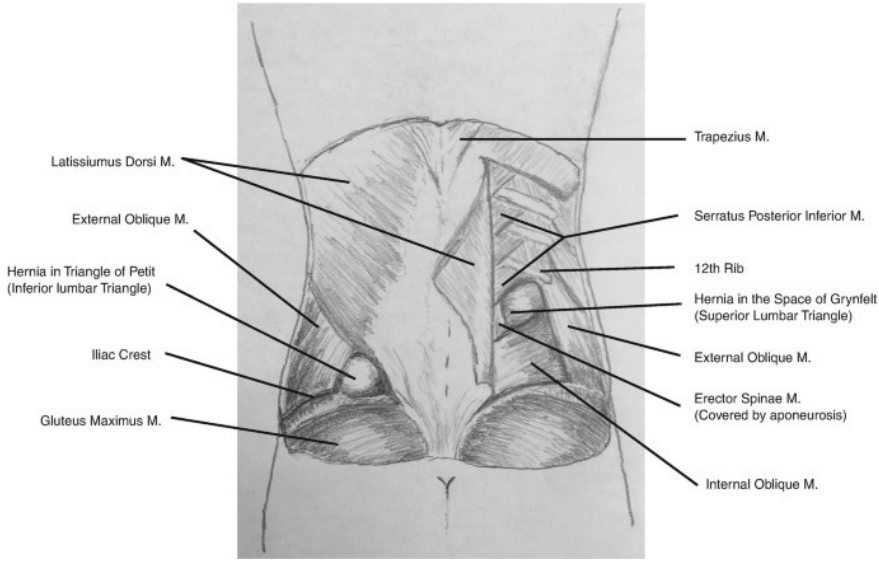


Picture 13: Spiegelian Hernia repair (11).

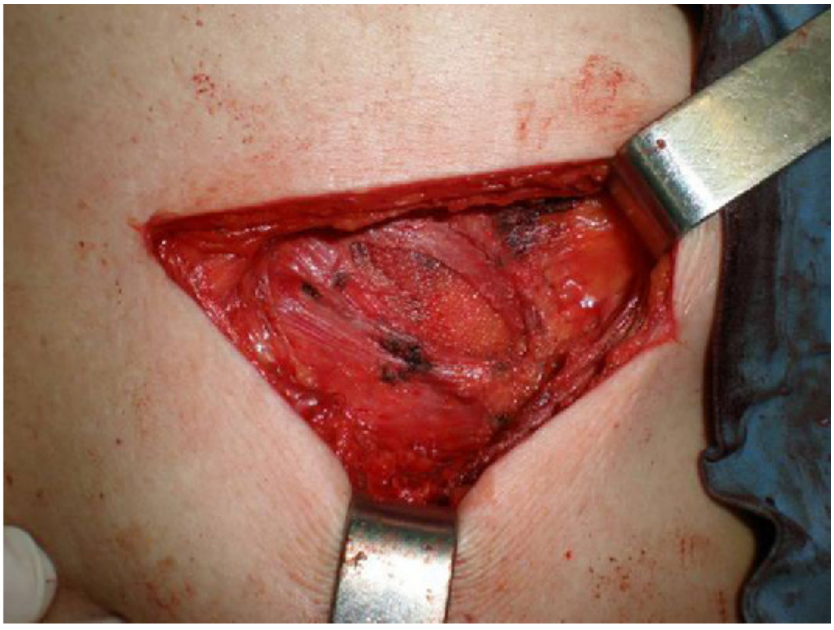
5.1.6. Lumbar Hernia

It is a very rare hernia type. (4) Lumbar hernia may occur in two areas of the posterolateral abdominal wall. Frequent one is the superior lumbar triangle of Grynfeltt. The inferior lumbar triangle of Petit is the other area but hernias from this area is rare (Picture 14). In large hernias the defect wall can affect both areas. (5,6)

According to lumbar hernia type, suitable repair sutures are done and a mesh is preferably placed to avoid recurrences (Picture 15).



Picture 14: Lumbar Hernia types



Picture 15: Inlay mesh repair for lumbar hernia. (12)

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CHAPTER IV

DIVERTICULAR DISEASE OF THE COLON

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1. Introduction

The term 'diverticulum' derives from the Latin word 'diverto', meaning turn aside. The English equivalent of the word is 'divertick', which means 'a small turn to the side', a pouch of limited size. A colon diverticulum is practically a herniation of the colon mucosa from the colon muscle layer. Therefore, colonic diverticular disease (DD) is an acquired condition. A luminal true diverticulum has been described as a diverticulum that includes all layers of the luminal canal wall, but in the colon this usually consists of an enlarged haustra. In Fifield's studies conducted in 1927 on 10,167 autopsies at the London Hospital, no real diverticulum was found. (1) When DD is pronounced, diverticulosis, diverticulitis and diverticular bleeding come to mind basically. (2) Figure-1 shows a cross-sectional schematic view of the diverticulum. (3)

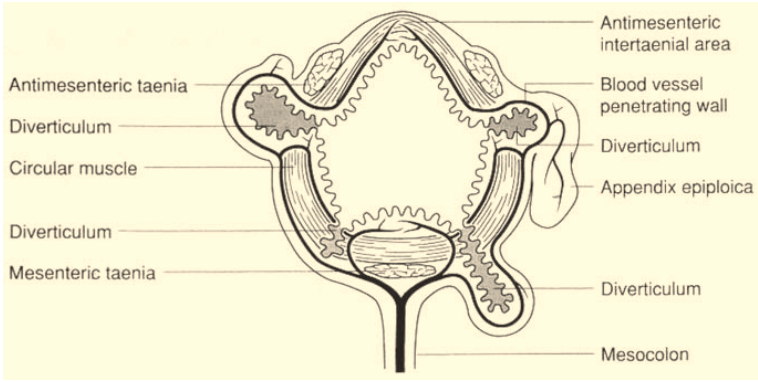

Figure-1: A cross section of the colon showing the relationship of the the diverticul with circumferential muscle layer and blood vessels. (3)

2. Brief History

The written history of problems with the intestines dates back to the Biblical Book of Judges, where abdominal injuries and problems of the pre-Christian Israelites are mentioned. A brief history of DD is summarized in Table-1 (4)

a) Celcus, 88 B.C.-A.D. 7: Information about the stoma
b) Littre, 1732: First identification as a diverticular hernia in a newborn autopsy
c) William Hunter and Matthew Baillie, 1793: Mention of 'DD' in a treatise on morbid anatomy
d) Fleischman, 1815: His use of the word 'divertikel' when describing this anomaly in the colon
e) Between 1815 and 1869, many authors of medical articles believed that this 'divertikel' was acquired, not congenital, and caused by constipation
f) Jones, 1859: His report that a fistula may be one of the associated complications of DD.
g) Beer, 1904: Identification of complications such as fistula, adhesion, stenosis, peritonitis
h) Telling and Grunner, 1917: The first classical textbook description of DD in England
i) Mayo, 1930: an estimate that 5% of patients over the age of 40 have diverticula in their colon
j) Smithwick, 1942: arguing that resection of the troublesome colon can be performed with minimal mortality, provided that the patient is fully evaluated and prepared
k) Hartmann, 1923: He developed the end colostomy, and this procedure was used in many hospitals as a two-stage procedure for the resection of DD, and it is still often used

Table-1: The history of DD. (4)

In the historical flow, a new consensus is developing towards a one-stage procedure in the 21st century, but the choice of a single or multi stage resection still remains the most controversial issue. (4)

Denis Burkitt, an Irish surgeon who worked in Uganda in the 1960s and 1970s, aroused great interest in the condition with his observation that this disease seemed to affect only the expatriate population, rather than the resident population. With the different diet between the two populations, the

"dietary hypothesis in the pathogenesis of diverticulosis" appeared. Burkitt et al. identified that there is an inverse relationship between colon passage time and fiber intake amount. In the hypothesis; it was suggested that higher transit times are associated with higher intraluminal pressures within the intestine, which in turn causes the characteristic acquired "blowing" vesicles observed in diverticulosis. (5)

3. Prevalence and Epidemiology

The prevalence of DD is highest in the Western world and/or in countries that follow a more Western lifestyle. DD affects 5-45% of individuals in the Western world depending on both the variability of diagnostic methods and the age of the individual. (6) In the United Kingdom, the United States and Australia, the incidence of DD of the colon was associated with age and national origin, and has increased from 5% to 50% since the beginning of the 21st century. The dramatic occurrence of the disease in Japanese people who migrated to Hawaii and in urban South African blacks suggests the predominance of environmental causes. (7) In general, the prevalence of DD increases with age, from 20% of affected individuals at the age of 40 to 60% of affected individuals at the age of 60. About 95% of patients with DD caused by the Western world have diverticula in the sigmoid colon. 24% of all patients with DD have a diverticulum mainly involving the sigmoid colon, 7% have a diverticulum evenly distributed throughout the entire colon, and 4% have a diverticulum only in the proximal sigmoid colon. (6) Based on radiological findings, in the United States, the incidence of colonic DD in the elderly has increased from 5% in 1930 to 30% in 1953. It has also been reported that between 1909 and 1975, the total raw fiber content of the American people's diet decreased by 28%. (7)

4. Etiology and Pathophysiology

Although DD is called a disease of Western industrialized civilization, it can be better described as a disease of welfare and refined food products. (9) Burkitt et al. examined the colonic transition times and stool weights in individuals with DD on different groups and reported that patients who increased fiber intake in their diet showed a decrease in symptoms. (5,8) In contrast, DD is rare in less affluent non-industrialized countries. However, DD is also unusual in Japan, where the population continues to consume a diet high in fiber. (9) The risk of hospitalization for acute diverticulitis (AD) is associated with modifiable risk factors. Factors that increase the risk of hospitalization in western regions

include obesity, high red meat intake, hypertension, hyperlipidemia, oral contraceptive use, hormone replacement therapy, smoking, and the use of some medications (such as aspirin, NSAIDs, and corticosteroids). Similarly, factors that reduce the increase in hospitalization include vigorous and regular physical activity, a high level of education, a high fiber intake, and a vegetarian diet. (10)

Diverticulum occurs in the weaker parts of the colon wall, where the vasa recta penetrates into the circular muscle layer. The vast majority of colonic diverticula are typically pseudo-diverticula. The mucosa and submucosa are herniated through a defect or weakness in the muscle layer and are covered with only serosa from the outside. True diverticulae are much rarer (e.g.: Meckel's diverticulum) and involve all layers of the intestinal wall (mucosa, muscle and serosa). (11)

An important predisposing factor for the formation of colonic diverticulum is abnormal colonic mobility (e.g. Intestinal spasms or dyskinesia), which results in exaggerated segmental muscular contractions, high intraluminal pressures and separation of the colonic lumen into chambers. The slow passage time of feces is the time it takes for the fecal contents to travel through the colon. This can help the formation of diverticulum, which protrudes at its weakest points under pressure. Solidification of the stool by staying in the colon for a longer period of time causes more pressure and difficulty in the evacuation of the intestines. (12)

Diverticulae are found in the sigmoid colon in 90% of all patients, and the sigmoid colon is the primary colon part in 50%. (13) Since the sigmoid colon is the segment of the colon with the smallest diameter, it is also the segment with the highest intraluminal pressure. Connective tissue disorders such as Marfan syndrome, diseases such as Ehlers-Danlos syndrome or autosomal dominant polycystic kidney disease can cause structural changes (weakness) in the intestinal wall and predispose a person to the formation of colon diverticulum. (6) Diverticulum tends to bleed due to the approach of the vasa rectum to the intestinal lumen as a result of herniation of the mucosa and submucosa through the muscle layer. With the formation of diverticulum, the vasa rectum is separated from the intestinal lumen by a mucous layer alone and exposed to a larger amount of injury. This results in eccentric intimal thickening, thinning of the medium and eventually segmental weaknesses along these arteries, which causes the vasa rectum to rupture and bleed towards the intestinal lumen. Diverticular bleeding typically occurs in the absence of diverticular inflammation or infection (i.e. diverticulitis). Diverticulitis, on the other hand, is typically caused by micro or macroscopic perforation of a diverticulum. This may or may not also be due to congestion (for example, with a stool). Increased intraluminal pressure or

thickening and condensing food matter ultimately causes diverticular perforation with inflammation and focal necrosis. The associated inflammation is usually mild, tends to close the holes of the pericolic fat and mesenteric diverticulum. This may or may not cause the formation of an abscess or fistula, or intestinal obstruction. In rare cases, the holes can be large and uncontrollable, leading to peritonitis. (6)

5. Symptoms and Evaluation

5.1. Diverticulosis

Non-inflamed colonic diverticulum is not considered a cause of abdominal pain or discomfort. In patients with abdominal pain and with a non-inflammatory diverticulum evidenced by a barium graph, the diverticulum is usually not the cause of the symptoms (Figure-2). A more reasonable explanation for the pain that occurs in patients with diverticulum is the excessive pressure applied by the segmentation of the colon. Although diverticulosis is considered in the differential diagnosis of a patient with intermittent mild to moderate lower abdominal pain, other diagnoses that should be eliminated include chronic constipation, diverticulitis, irritable bowel syndrome and colon adenocarcinoma. Irritable bowel syndrome is considered by some authors to be a peridiverticular condition and is a diagnosis made by exclusion. (9)

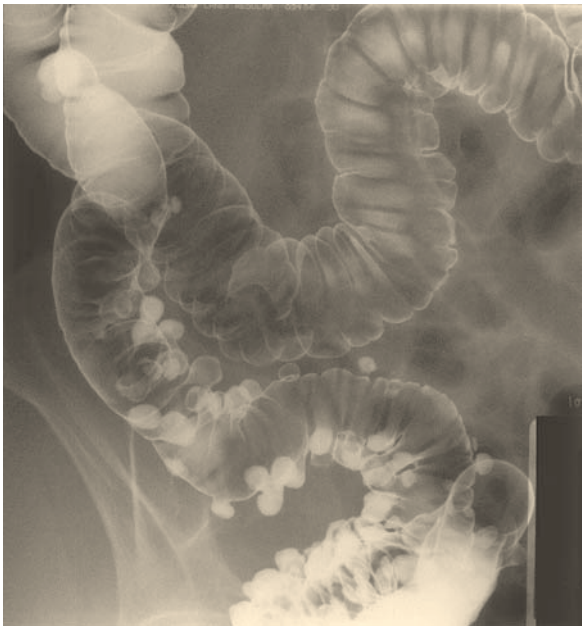

Figure-2: Barium enema and multiple colonic diverticulae. (9)

5.2. Diverticulitis

AD may develop when a blockage occurs in the diverticulum neck. (Figure-3) This can lead to an overgrowth of bacteria and local ischemia, and then an episode of acute inflammation may develop. AD affects from 4% to 25% of patients with diverticulosis. Diverticulitis is rare in those under the age of 40 (<5%), and more than half of young diverticulitis patients are obese. The clinical presentation is non-specific and includes left or right lower quadrant pain, bloating, fever, nausea, vomiting, tachycardia and even a change in bowel habit. Left-shift leukocytosis occurs in about 55% to 60% of patients. (14) Depending on the exact location of the inflammation and whether there is a perforation of the free abdomen, abdominal pain and tenderness may vary significantly. It is often difficult to distinguish diverticulitis with free perforation and generalized peritonitis from other causes of internal luminal organ perforations. The suspicion of diverticulitis increases when the process is localized in the lower left quadrant and there is a palpable, tender mass. (9)

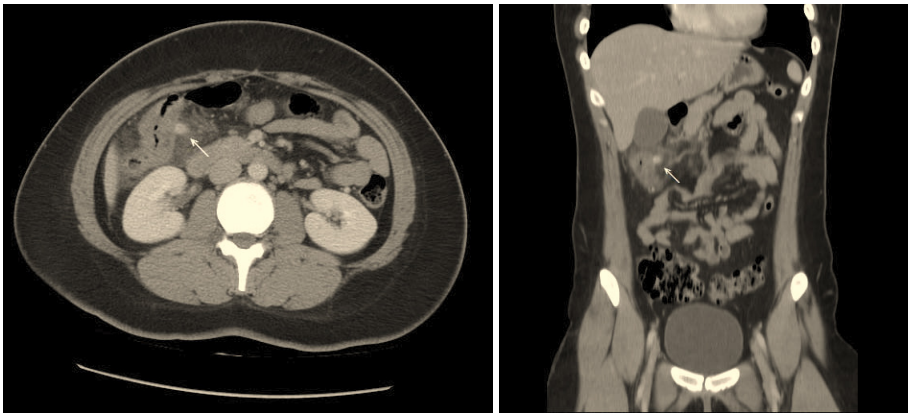

Figure-3: Upper image: Colon diverticulitis (wall thickening and fat bending) on a horizontal CT image (arrow). Bottom image: Coronal cross-sectional CT image of the same patient. (15)

5.3. Haemorrhage-bleeding

A less common but serious complication of DD is colonic diverticular bleeding (CDB). Mucosal ulceration caused by an inflamed diverticulum can erode towards one of the vessels of the vasa rectum and cause it to bleed. Characteristically, this bleeding is vivid, painless and bright red. Minor bleeding may be caused by small mucosal ulceration. Although CDB is a rare complication of DD, it accounts for about 40% of cases of lower GIS bleeding. (5)

CDB can occur with diverticulosis or diverticulitis. Hematochesia is rarely reported in those with AD, but massive bleeding is more typically associated with diverticulosis (Figure-4). (9) It is important to distinguish CDB from colonic angiodysplasia, patients bleeding from angiodysplasia and diverticulosis are usually asymptomatic before bleeding, and blood loss can be excessive in both cases. Patients who develop massive bleeding secondary to inflammatory bowel disease (IBD) usually have a history of colitis. Sometimes a patient with colitis shows a fulminant clinic and has no history of the disease. Ischemic colitis is usually manifested by abdominal pain, diarrhea and a history of vascular occlusive disease in other regions of the abdomen. Various other causes of massive upper gastrointestinal bleeding should always be questioned in the differential diagnosis of lower gastrointestinal bleeding. (9)

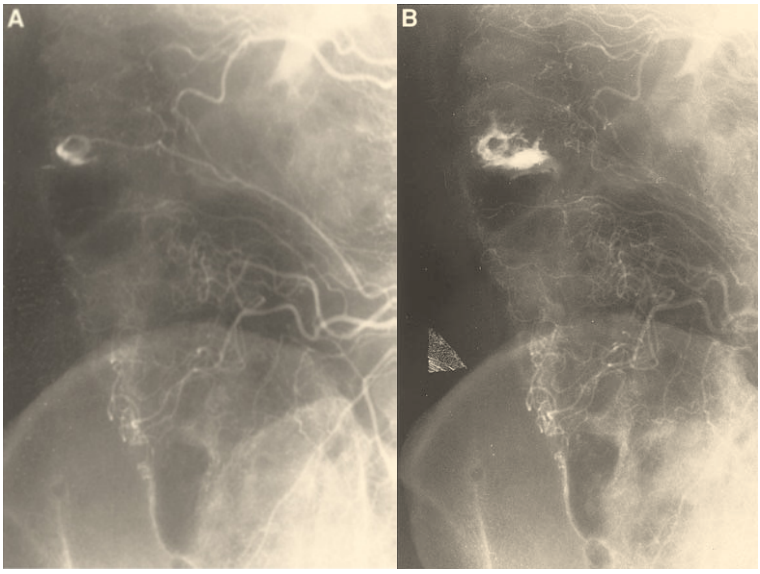

Figure-4: Upper mesenteric arteriogram of a patient with bleeding from the right colon diverticulum. ((A) Early X-ray vision with contrast material showing the diverticulum (top left). ((B) A late X-ray vision showing the overflow of contrast material into the lumen of the colon. (3)

In unstable hemodynamic condition, resuscitation should be initiated immediately. Diagnostic tests or other therapeutic interventions can be initiated later. Determining the source of the bleeding is important to determine the intervention to be performed. Most CDB episodes stop spontaneously, but they recur at a high rate. (14)

5.4. Obstruction

Symptoms of intestinal obstruction are found in about a quarter of whole patients with diverticulitis who need to be hospitalized. This complication may be due to fibrosis of the sigmoid colon caused by recurrent episodes of diverticulitis or paralytic ileus due to pus in the peritoneal cavity. Organic narrowing of the colon due to scarring can cause a structure that cannot relax even after propanthelin is given. This can make it difficult or impossible to be sure whether the resulting blockage is due to diverticulitis or cancer. (1) The relatively high incidence (7%) of adenocarcinoma in patients with sigmoid DD and the relative difficulty of diagnosing adenocarcinoma of the colon when a large phlegmonous mass is present is an important problem in the evaluation of patients with sigmoid colon obstruction. (9)

6. Diagnosis

If DD (including AD) is suspected, the first stage is to take a detailed medical history and perform a physical examination to assess the disease outcomes and factors affecting treatment, such as comorbidities and medications, and to evaluate indicators of disease severity, such as fever-peritonitis. (10)

6.1. Contrast enema

This was the preferred method for investigating diverticulitis before computed tomography (CT) scanning became widespread. (5) In acute cases, barium enema should not be used due to the risk of barium peritonitis, which has a high mortality rate (50%). Also, the use of barium may distort the images of subsequent endoscopy, sonography or computed tomography. (7) In addition to the saw-tooth effect caused by shortening of the muscularis propria, there are characteristic bursting appearances of diverticulosis in contrast enema (Figure-2). In addition, complications of the disease can be shown with this examination. An important limitation of this technique is that sometimes the severity of DD is such that the presence of a carcinoma in the diverticular area will be hidden and will not be diagnosed unless further research is conducted. In this case, a mandatory luminal examination should be performed. (5) Today, this method has been replaced by computed tomography.

6.2. Computed tomography scan

If the patient presents with extreme abdominal pain, the preferred test to prevent / avoid the risk of intestinal rupture in an environment of intestinal

infection or inflammation is typically computed tomography (CT) scan. (15) CT scanning has largely overtaken contrast enema as the gold standard research of choice for the treatment of DD in particular, as well as acute abdominal in general. It has the highest specificity and sensitivity of any modality for the diagnosis of AD, and also provides accurate information about the associated complications of the disease. (16) It is an important aid to surgical colon resection for an associated abscess and usually reduces the need for a two-stage colectomy. (7) CT findings suggestive of AD include the display of the diverticulum itself, associated inflammation in pericolic fat, pericolic abscesses and peritonitis, as well as free perforation and distant inflammatory foci. Screening is usually performed by the application of oral and intravenous contrast to increase the sensitivity of the diagnosis of small holes. The application of rectal contrast can help diagnose fistulas, as well as reach up to the site of peridiverticular abscess and mechanical intestinal obstruction and help diagnose them. (5) However, one study found that the use of rectal contrast in combination with oral and intravenous did not have a significant advantage and was therefore negligible in patients with suspected DD. (17)

6.3. Ultrasound scan

Abdominal ultrasonography is a preferred imaging method as it is cheap and non-invasive. However, it is an operator-dependent method and has a lower competence in assessing the lumen organs and excluding other causes of abdominal pain. (18) In the right hands, ultrasound can be a very sensitive form of research in diverticulitis. (19) Hypoechoic peridiverticular inflammatory reaction, detection of peridiverticular or wall abscess, thickening of the intestinal wall by more than 4 mm in the area of abdominal tenderness and the presence of diverticulum in other parts of the intestine are among the ultrasonographic findings that support the diagnosis of AD. (18)

6.4. Endoscopy

Endoscopy plays a role in the diagnosis of nonspecific GI symptoms and is superior to CT scanning in understanding the difference between a benign and a malignant structure. Routine endoscopic examination of patients will regularly reveal an uncomplicated diverticular orifice(s) located between the normal mucous ridges. (5) Colorectal cancer (CRC) may rarely present with signs and symptoms similar to those of acute complicated diverticulitis and may have similar CT findings with an estimated imaging overlap of 10%. Given the guidance on screening intervals for the general population; the known relatively

stagnant natural history of colonic neoplasms; and the fact that colonoscopy is associated with harms, physical loads and costs, it makes sense to extend the acceptable period beyond 1 to 2 years from the previous colonoscopic evaluation. (20) An endoscopic view of diverticulosis is available in Figure-5. (21)

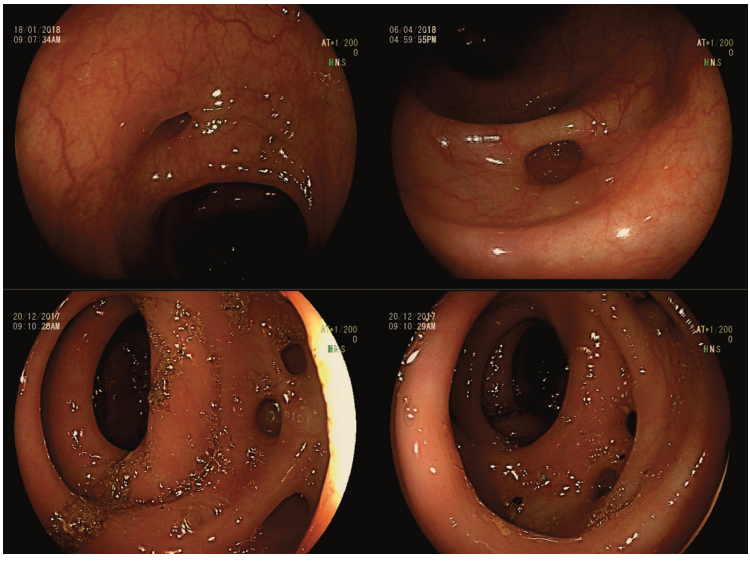

Figure-5: Endoscopic visualization of diverticulosis. (21)

Diverticulosis and colon polyps are common findings during colonoscopy. The presence of colon polyps with DD can lead to an increased risk of CRC. There is no consensus on the relationship between colon diverticulosis and colon polyps. In a study of J. Ray et al, the presence of colonic diverticulosis in any part of the colon was found to be associated with an increased incidence of adjacent colon polyps. It has been noted that diverticulosis and polyps in the right colon are more than usual, and although the prevalence of colon diverticulosis with adenomatous colon polyps is higher, the incidence of CRC is not higher. (22)

7. Differential Diagnosis

Diverticulosis is manifested by rectal bleeding, and most often this is the only symptom that occurs. The differential diagnosis includes: Hemorrhoidal disease, ulcers on the intestinal wall, IBD, anal fissure, anal abscess or fistula, colon polyps, colon cancer, constipation, radiation therapy, angiodysplasias, colitis, proctitis, ischemic colon, appendicitis, pelvic inflammatory disease, urinary system diseases. (6,7)

8. Management and Treatment

Non-surgical treatment of patients with acute left-sided colonic diverticulitis (ALCD) remains largely unanswered. Very few adequately conducted studies have addressed the need for hospitalization of patients with uncomplicated disease or the value of percutaneous drainage for patients with diverticulitis complicated by abscesses. While the findings are probably generalizable to all patients involved, there is little evidence to guide decisions about which patients should receive various treatment options. There is a compelling need for well-conducted studies that address the effectiveness and harms of interventions and the heterogeneity of treatment effect. (23)

8.1. Symptomatic uncomplicated diverticular disease

Symptomatic uncomplicated diverticular disease (SUDD) can be defined as a chronic condition that impairs quality of life, characterized by persistent left lower quadrant abdominal pain with bowel movement changes and low-grade inflammation, but without systemic inflammation. (Figure-6) (24) The pathogenesis of SUDD is still unclear: low-grade inflammation, changes in the fecal microbiota, abnormal colonic mobility, colonic mucosal ischemia and neuro-immune interaction have been identified as potential factors leading to the development of symptoms. The use of rifaximin, fiber and mesalazine shows potential to control symptoms in patients with SUDD and may prevent AD. Surgery may be considered in patients with medical treatment failure and persistent quality of life disorders. (24)

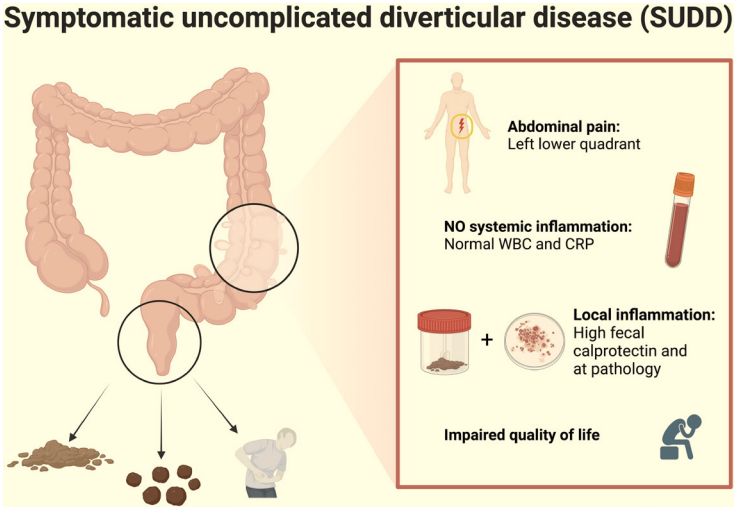

Figure-6: SUDD (24)

8.2. Classi ication

Colonic AD is a worldwide health problem as one of the most common diagnoses in emergency departments and the leading cause of elective colonic resection. Approximately 5-25% of patients with colonic diverticulosis will develop an AD attack, 85% of these attacks will be uncomplicated. Complicated AD involves the development of intra-abdominal peritoneal infection and perforation. Currently, the three most popular scoring systems based on radiological findings are modified Hinchey, AAST and WSES classifications. These scorings have similar results in predicting complications, re-intervention and mortality rates. According to a current study, AAST and modified Hinchey scores were found to provide the most appropriate result for predicting the need for surgery and the occurrence of major complications. (25) Hinchey's scoring separating the five stages of AD (Table-5) is widely used worldwide. (26)

Stage 0: clinically mild diverticulitis
Stage Ia: pericolic inflammation
Stage Ib: pericolic or mesocolic <5 cm abscess
Stage II: intra-abdominal, pelvic or retroperitoneal abscess or abscess distant from the primary inflammation
Stage III: generalized purulent peritonitis
Stage IV: fecal peritonitis

Table-2: Hinchey's classification for AD. (26)

Treatment goals in AD include regression or relief of symptoms and inflammation, prevention of complications and recurrence. A summary algorithm related to this is presented in Figure-7. (26)

8.3. Medical treatment, dietary modifications

Conservative & medical treatment of AD is somewhat controversial. A systematic review by Dichman et al based on randomized controlled trials published in 2022 investigated whether antibiotic treatment of uncomplicated AD has an effect on the development of complications or emergency surgery. According to the detected records, no significant effect of the tested antibiotic treatments has been detected. It has been reported that there is no difference between single antibiotics compared to dual therapy, and there is also no difference between the defined short and long intravenous antibiotic therapy.

In meta-analyses comparing antibiotic therapy with conservative therapy, including about 1300 participants, there was no statistical difference in clinical outcomes. (27)

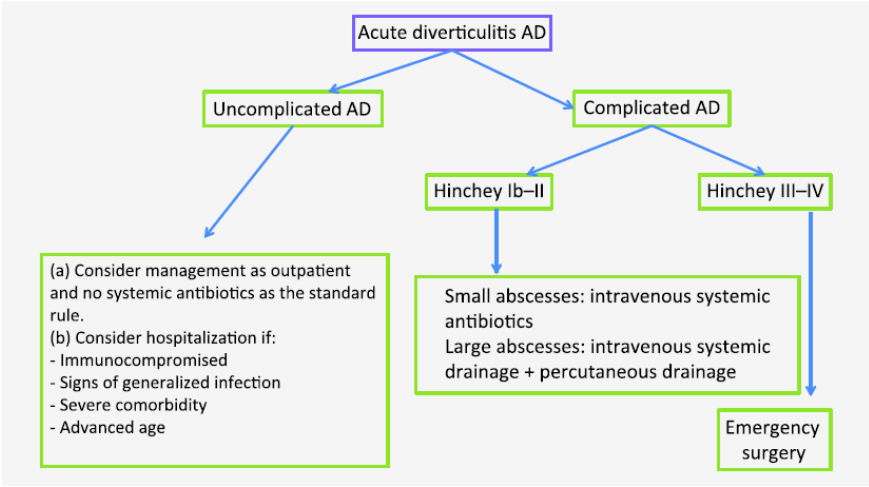

Figure-7: Algorithm defining current therapeutic strategies for AD. (26)

The study of Some et al. showed that, patients with uncomplicated diverticulitis need about four days of intravenous antibiotics and hospitalization for eight days. As a result, the strategy of reviewing treatment on the third day of hospitalization for uncomplicated diverticulitis was able to safely reduce the duration of antibiotic use without increasing complications compared to the treatment chosen by the doctor, and increase the proportion of patients who completed treatment with three days of antibiotic use. (28)

According to a meta-analysis published by Fowler et al. in 2021; it was found that failure rates following non-surgical treatment of AD complicated by abscess have not significantly decreased over the past three decades. (29)

Bolkenstein et al. have argued that conservative treatment is an appropriate treatment strategy for patients with AD with isolated pericolic air. However, it remains unclear whether antibiotic therapy is necessary in patients with isolated pericolic air due to the low number of cases. (30)

According to Sallinen et al, the non-surgical treatment of perforated diverticulitis with generalized clinical peritonitis with a small amount of free intraperitoneal air or with the absence of fluid in the Douglas cavity is safe and effective with a success rate of 86%. Thet concluded that patients with pericolic air without abscess can be treated without surgery with a 99% success rate. (31)

As a summary of these various and contradictory results, it can be said that Hinchey Ia and Ib cases can be treated medically-conservatively (percutaneous drainage, follow-up, etc.) by taking into account other characteristics of the patient.

Considering that diet and lifestyle are effective in the development of this disease, the progression of the disease can be stopped with strict control of these parameters.

According to Carabotti et al.'s systematic review, authors focused on dietary habits as potential risk factors for diverticular complications such as AD or diverticular hemorrhage. Unlike previous systematic reviews, the role of different dietary components (dietary fiber, meat, alcohol and coffee consumption) or dietary pattern and the risk of complicated DD were tried to determine. High fiber intake has been associated with a reduced risk of diverticulitis or a reduced hospitalization due to DD, whereas conflicting results have been found about the increased risk of diverticulitis with a general western diet, high red meat consumption and alcohol use. (32)

Lukosiene et al. found that advanced age, a feeling of incomplete bowel emptying and a high level of education were associated with the risk of diverticulitis in CD patients. (33)

According to study of Polese et al., it was stated that DD patients had the total required daily intake of calories, fats and vitamins compared to control subjects, and patients with a history of diverticulitis had the lowest consumption of both soluble and insoluble fiber. It is emphasized that a balanced diet potentially affects the intestinal microbiota, which is a key factor in the pathogenesis of DD. (34)

In the light of ongoing current studies and classical information, the role of diet in stopping and regressing DD is obvious.

8.4. Surgical treatment

The decision of whether to operate or not of patients with DD should be personalized based on the latest evidence. Plausible surgeons today should thoroughly explain and discuss the issue to patients and their relatives about the uncertain benefits and potential risks of different surgical treatments and surgical access before performing an elective or emergency intervention. (35)

8.4.1. Elective surgery, laparoscopic intervention

It is known that elective sigmoid resection for DD should be avoided except in cases of stenosis, fistulization to a neighboring organ or bleeding. However,

Vaghiri et al. in a meta-analysis dated 2022, state that the timing of sigmoid resection in DD is still a matter of debate. (36) The risk of perforation may be five times higher in high-risk patients with episodes of diverticulitis who are under immunosuppressive therapy, have chronic kidney failure or collagen-vascular diseases, and are treated conservatively. Such high-risk patients should be considered as good candidates for elective sigmoid resection. (37) The optimal timing of laparoscopic sigmoid resection should be adapted to the clinical features of complicated DD. Early elective laparoscopic sigmoidectomy can be performed safely in acute uncomplicated stages of DD. The higher risk of conversion to laparotomy in cases with acute or recurrent diverticulitis complicated by fistula, stenosis, large abscess or stenosis formation (Complicated DD types 2b and 3c) justifies a delayed approach to a non-inflammatory attack six weeks after the first attack, when clinically possible. (38)

8.4.2. Emergency situations

It is still controversial whether the Hartmann procedure (HP; primary resection + end stoma) or primary anastomosis with / without a diverting ileostomy is performed in the treatment of complicated / perforated diverticulitis. (39,40) It has been reported that the preference for laparoscopic lavage instead of primary resection in perforated diverticulitis is not widely accepted. (41-45) In this type of patients, damage control surgery + luminal diversion provides rapid cleaning of the septic focus and rapid intervention in generalized peritonitis. (46) Sigmoidectomy and primary anastomosis as a treatment for perforated diverticulitis in hemodynamically stable, immunocompetent patients are superior to HP in terms of long-term stoma absence rate, overall hospitalization rate, parastomal hernias and life expectancy with stoma. (47) In a current study, it was stated that patients treated with emergency surgery due to perforated diverticulitis with purulent peritonitis continue to experience problems with intestinal dysfunction in the long term, regardless of intestinal continuity or permanent stoma by the method to be applied to emergency cases. (48)

8.4.2.1. Haemorrhage-bleeding

Bleeding points can be localized by the interventional radiology team with digital susbstraction angiographic techniques, but the success of this technique depends to some extent on the rate of blood loss, and the optimal rate is 0.2–0.5 ml/minute. Once identified, it is possible to embolize the bleeding point in order to prevent a major surgical procedure in an already compromised patient. If this service is not available, perooperatory colonoscopy is an alternative approach;

however, vision may be blocked by luminal blood. (5) A large multicenter study concluded that endoscopic treatment of definitive CDB is the most effective in preventing short- and long-term recurrence compared to not treating definitive CDB or presumptive CDB. Endoscopists should try to find and treat signs of recent bleeding in patients with suspected CDB. (49) An endoscopic intervention is seen in Figure-8. (14) Confirmed CDB has high frequencies of transfusion, invasive treatment and early re-bleeding. The right CDB shows higher transfusion and invasive treatment rates than the left CDB. Hypertension is a risk factor for chronic kidney disease and late re-bleeding of past CBD. (50)

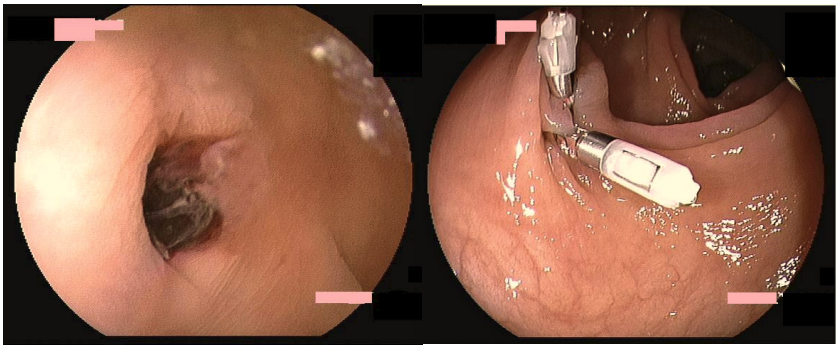

Figure-8: Left photo: blood clot and diverticulum. Right photo: Two hemoclips were applied and hemostasis was obtained in the same patient. (14)

9. Prognosis and Complications

Uncomplicated sigmoid diverticulitis usually has a good prognosis. About 13% of patients have one relapse episode and less than five percent have a second relapse. Young age (≤ 50 years old), severe diverticulitis on computed tomography, pelvic abscess and functional bowel disease diagnosis before elective colectomy cause poor long-term consequences. (14) Diverticulitis is complicated by abscess, fistula, intestinal obstruction or free perforation. Inflammation within the diverticulum can lead to the formation of a fistula between the colon and adjacent internal organs.

Fistulas are most commonly colovesical or colovaginal. Colovesical fistula is manifested by pneumaturia, fecaluria or dysuria. Patients with colovaginal fistula may experience vaginal passage of feces or gas. (6) Colovesical fistulas account for about half of the fistulas secondary to diverticulitis. In patients with diverticular coloenteric fistula, diarrhea, abdominal pain, abdominal tenderness,

abdominal distension and pelvic mass sensation are observed. (9) Rectal contrast CT scan is the most sensitive test for the presence of colovesical fistula.

The preferred operative management of an uncomplicated coloenteric fistula is en-block resection of the relevant small bowel segment, fistula and diseased colon segment. Then, primary anastomoses of both the small intestine and the colon are performed. If there are complicating factors, such as other fistulas, intra-abdominal abscess or insufficient intestinal preparation secondary to obstruction, primary anastomosis of the small intestine is performed as the first stage of a two-stage procedure, along with the formation of colostomy / ileostomy. (9)

10. Stoma and Stoma Reversal

Stoma is derived from the classical Greek word meaning 'mouth' and is used as a medical term meaning 'artificial opening'. (50) Careful placement of a stoma, whether temporary or permanent, plays an important role in the rehabilitation of the patient. The areas to be avoided when placing a stoma are given in Table-3. (51)

* Waist line
* Hip bones
* Previous scar lines
* Groin areas
* Fat folds and bloating
* Umbilical cord
* Existing fistula and drainage areas
* Under the sagging breasts
* Primary incision site
* Areas with skin problems such as psoriasis
* Areas crossed by straps for artificial limbs or other surgical instruments
* Areas where the stoma would be difficult if there was weight loss or gain

Table-3: Areas of the body that should be avoided when opening a stoma. (51)

In a multicenter study comparing HP and primary anostomosis + proximal diversion (PAPD), it was found that patients with PAPD are more likely to be re-hospitalized within 90 days of discharge and complications of stoma closure are high. After discharge following the initial admission, patients with PAPD

were subjected to more frequent unscheduled readmissions, but stoma closure rates were found to be higher. (52) In one study, it was found that patients with purulent perforated diverticulitis (Hinchey stage III) who underwent segmental resection and primary anostomosis had lower morbidity rates and higher rates of stoma closure compared to those who underwent HP. (53) In another study, the rate of major complications in patients undergoing stoma closure surgery was relatively low (12%): anastomosis leakage was found in 3%, and mortality was found to be 0%. However, according to the results of the study, HP remains a suitable option for high-risk patients with perforated AD. (54)

In summary, a fifth of patients are left with a permanent stoma after HP due to AD, although the stoma survives long enough to be closed. These patients are mostly older, high-risk patients who need help with their daily routine lives.

11. DD of Cecum and Right Colon

The incidence of true diverticulum is higher in the cecum and the right colon than in the rest of the colon, but false diverticulum is still dominant in the left colon. The true diverticulum tends to be solitary and arises from the anterior cecum close to the ileocecal valve. It occurs in only 1-2% of the population. Right-sided diverticulosis (RCD) is also seen in 7-30% of people with left-sided diverticulosis (LCD). (9) RCD is becoming increasingly common. As a general literature information, RCD has been described as a rare congenital finding in Asian populations. (55) Patients with RCD are younger and the disease course is more benign than LCD. The clinic can be confused with appendicitis without proper imaging. In the rare cases where emergency surgery is required, RCD is associated with lower operative morbidity and mortality compared to LCD. (56)

According to one study, surgical treatment and conservative treatment methods for acute RCD have been indicated to be both safe and effective. Surgical treatment should be considered mainly for patients with recurrence risk factors (with a previous history of RCD) or complicated acute RCD. (57) According to another study, it was stated that conservative treatment is effective for RCD and LCD with low recurrence rates and treatment failure, but LCD shows a higher recurrence rate. (58) Both the incidence and complication rate of RCD are lower than LCD. Conservative treatment of RCD is the primary choice. (59)

12. Colonoscopy After Acute Attacks and Follow-Up

There are various opinions about performing a colonoscopy after a diverticular attack and its remission. Sallinen et al. recommended routine colonoscopy after a diverticular abscess treated without surgery to exclude colon cancer in the affected part of the colon. They also reported that patients undergoing operative treatment for diverticular abscess should have a colonoscopy before surgery to exclude the perforation of CRC, while routine colonoscopy after uncomplicated AD is unnecessary in the absence of other risk factors. (60) Andrade et al. claim that patients with uncomplicated diverticulitis diagnosed on a CT scan are not at high risk for CRC. Accordingly, an episode of uncomplicated diverticulitis diagnosed on CT does not seem to be a recommendation for colonoscopy on its own. In patients older than 50 years who have not had a screening colonoscopy and have CD (abscess or other suspicious signs such as a mass), colonoscopy should be recommended, given the increased risk of malignancy. This more selective approach will allow for more efficient use of limited resources for CRC screening. (61) Mari et al. recommended routine colonoscopy in patients with a history of active smoking with the male gender. They also recommend that follow-up colonoscopy after an AD episode should be individualized according to potential risk factors. (62) According to another opinion, colonoscopy should be performed in patients who have had a complicated attack or who remain symptomatic after an uncomplicated attack due to an increased risk of CRC after AD. (63) Patients with colonic diverticulum, who are at a higher risk of dysplastic lesions, may require more careful endoscopic surveillance than the general population. (64) Colonoscopy recommendations of Tursi et al. are included in the 2022 review. Accordingly, colonoscopy in DD should be performed under the conditions in Table-4. (65)

13. Special Situations

13.1. Segmental colitis associated with diverticulosis (SCAD)

SCAD is a clinical entity with macroscopic and microscopic characteristics characterized by chronic mucosal inflammation involving the interdiverticular mucosa, typically the sigmoid descending colon, and protecting the proximal and rectal colon. Generally, men are affected more than women, and the average presentation age is 63.6 years. The most common clinical signs are rectal bleeding, diarrhea and abdominal pain. Biochemical changes such as weight loss, nausea, fever and leukocytosis are very rare. The majority of these patients

regress spontaneously or respond to 5-aminosalicylates. (66) The diagnosis of SCAD poses a difficulty in clinical practice due to the heterogeneity of endoscopic findings and the lack of specified histological criteria.

1) In patients with lower gastrointestinal tract bleeding with suspected diverticulum, within 24 hours and with intestinal cleansing
2) It should be performed after at least seven days of treatment and only by cleansing with enemas, but in persistent symptomatic patients following a recent AD to exclude other diseases (CRC or IBD)
3) After the regression of an uncomplicated AD, if a quality examination of the colon has not been performed recently, 6 weeks after an acute attack
4) After the regression of a complex AD attack, which will always be performed 6 weeks after an acute attack
5) For patients diagnosed with the first endoscopic DD, with the application of existing endoscopic classifications in order to have a predictive value on the outcome of the disease

Table 4: DD and colonoscopy recommendations (65)

13.2. Multifocal disease

In Europe and North America, 15% of DD patients have right colon involvement and 7% of patients have pan-colonic involvement. Multifocal diverticulitis, bleeding or perforation is extremely rare and has only been reported anecdotally. The management of this disease should be individualized to the patient. If it is determined that a patient has more than one area of diverticulosis, but is symptomatic only from a separate part of the colon, treatment should follow the general principles of diverticulitis, attempting conservative treatment for uncomplicated disease and surgical or percutaneous intervention for more complex disease. Large colon resections are usually not necessary for asymptomatic multifocal DD detected incidentally. (67)

13.3. Recalcitrant diverticular abscess to medical treatment

The management of intra-abdominal diverticular abscess is still controversial. Conservative treatment is currently recommended for small abscesses (<4 cm), while percutaneous drainage (PD) or surgery is recommended for larger abscesses. (68)

13.4. Advanced age patient management

AD management is difficult in elderly patients (>65). Conservative treatment is safer and more effective in elderly patients in terms of preventing unnecessary surgeries from causing unexpected complications due to comorbidities (69)

14. Conclusions

To summarize the colonic DD; (70)

1. Diverticular colonic disease is most commonly seen in the sigmoid colon.

2. The association of abdominal CT and CRP is very useful in predicting the clinical severity of AD.

3. Contrast-enhanced abdominal CT is the gold standard in the diagnosis and staging of ALCD patients.

4. In the absence of widespread intraabdominal fluid in CT and in the presence of free air, conservative treatment is recommended, subject to close observation and follow-up of the patient.

5. Conservative treatment applied to patients with uncomplicated colonic DD consists of antibiotic therapy, intravenous hydration and fluid-electrolyte imbalance.

6. In patients with multiple comorbidities, hemodynamic instability, HP for the treatment of acute peritonitis caused by perforated colonic diverticulitis, in hemodynamically stable patients without comorbidity, resection + primary anastomosis with or without a stoma is recommended.

7. In patients with uncomplicated AD confirmed by CT, a routine evaluation of the colon is not recommended, while in patients with diverticular abscess treated without surgery, it is recommended to evaluate the colon no earlier than 4-6 weeks after acute healing.

8. Emergency laparoscopic sigmoidectomy is recommended in patients with diffuse acute peritonitis caused by perforated AD only if technical experience and skills are available with adequate equipment.

9. In patients with acute diffuse peritonitis due to diverticular perforation, lavage and laparoscopic drainage are recommended only in some selected patients.

10. The diagnosis and treatment principles of patients with acute RCD are similar to those of patients with acute LCD. However, complications

requiring surgery are higher in patients with acute LCD than in patients with acute RCD.

Elective colectomy for recurrent diverticulitis remains a decision whose practical consequences for both surgeons and patients differ little. (71)

However, the diagnosis and treatment of complicated CD has shifted from a surgical initial approach to a more conservative drainage and monitoring approach in recent years. With more studies, our ability to fine-tune intervention in this difficult disease process will improve.

If it is generalized; in the light of current information, a minimally invasive approach is recommended for patients requiring emergency or elective surgery as much as possible. (72)

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CHAPTER V

MASTITIS

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1. Introduction

Mastitis is inflammation of the breast tissue. A variety of factors can cause it, such as bacterial infection during lactation, injury to the breast without bacterial infection, infection of the skin around the breast.(1,2) The condition is predominantly observed during breastfeeding.(3) Mastitis is classified as lactational mastitis and nonlactational mastitis.(4)

2. Lactational Mastitis

Lactational mastitis is inflammation of the breast that develops during breastfeeding. Although this type of mastitis is thought to occur as a result of damage to the skin barrier due to breastfeeding, the exact mechanism is still controversial.(2) Some studies have found that breast milk has its own microbiota, apart from the breast skin and the newborn's oral flora.(5) This condition predominantly manifests within the initial six weeks postpartum. Etiological agents most commonly include Staphylococcus aureus, yet Staphylococcus epidermidis, and Streptococcus species also play roles.(5,6) Methicillin-resistant Staphylococcus aureus (MRSA) is also one of the important factors in lactational mastitis.(3) Nipple cracks, inadequate breastfeeding, and inappropriate brassiere usage are some of the other factors that increase the risk.(7)

Diagnostic criteria predominantly rely on historical and clinical examinations. In addition to breast tenderness and pain, swelling, increased temperature and redness, systemic findings such as fever and fatigue may also

accompany in advanced cases. It may cause abscess formation in the breast. Mastitis rarely causes sepsis. It can reduce milk synthesis and affect milk content.(1,8)

Laboratory tests, milk culture and blood culture are not routinely used in diagnosis. They can be used in severe cases or non-responsive instances. Although imaging methods are not routinely required; they can be used when there is no response to treatment, in cases of suspicion of abscess or as an aid in differential diagnosis. Ultrasonography is the preferred imaging method for mastitis.(4,7)

The differential diagnosis should encompass engorgement, duct narrowing, galactocele, and inflammatory breast cancer. Engorgement results from the physiological filling of the breast with milk. Bilateral fullness of breasts can be seen in the first days after the birth and relieves within a day. Duct narrowing is a sensitive and painful mass resulting from milk duct obstruction due to localized edema, but it is not accompanied by systemic findings. Galactoceles are soft cysts that occur due to milk retention. There is no tenderness and it can be easily detected by ultrasonography. Inflammatory breast cancer can be distinguished by different findings such as orange peel appearance and axillary lymphadenopathy. (9)

Lactational mastitis is usually self-limited. Symptoms are often relieved with oral antibiotherapy and supportive treatment. Milk secretion may decrease due to the mastitis. However, breastfeeding should continue. Hot or cold compress, paracetamol or ibuprofen can be used to treat pain.(4)

Caution is needed in cases that don't show improvement within two days of supportive treatment. Drainage should be provided in case of abscess development along with antibiotic treatment. Dicloxacillin, flucloxacillin, or cephalexin can be used as first-line treatments. Trimethoprim-sulfamethoxazole or clindamycin can be used in patients who are at risk for MRSA. In severe infections, vancomycin, ceftriaxone,and piperacillin-tazobactam can be used. (4,7,10)

3. Nonlactational Mastitis

3.1. Periductal Mastitis

Periductal mastitis is characterized by inflammation of the subareolar ducts. Etiology is unknown and it is unrelated to lactation. Generally, anaerobic bacterial infection is involved. Periductal mastitis is more common in young women, especially those who smoke.(11)

Diagnosis is made with clinical findings similar to lactational mastitis. In case of purulent discharge, culture can be taken. A differential diagnosis should be made between duct ectasia and breast cancer. Duct ectasia is more common in older age.

Although it usually has a chronic course, recovery can be achieved with antibiotic therapy. If an abscess forms, surgical drainage or aspiration should be performed. Amoxicillin-clavulanate, dicloxacillin, flucloxacillin or cephalexin are used for antibiotherapy. Metronidazole can be added if anaerobic agent is suspected. Surgical treatment may be considered in cases of subareolar abscess or periareolar fistula due to recurrent mastitis. Surgical excision of the affected duct can be performed.(4)

3.2. Idiopathic Granulomatous Mastitis

Idiopathic granulomatous mastitis (IGM) a very rare condition of mastitis of unknown etiology. It can be confused with cancer because it usually presents as a solid mass in one breast, but it is a benign condition. It is more common in young women who have given birth. It is suggested that it might be associated with autoimmunity or Corynebacterium infection.(12,13)

Due to its clinical presentation, ultrasonography is used as the first-line imaging mostly. After distinguishing between mass and abscess on ultrasonography, biopsy is required for histopathological diagnosis. Histopathology shows noncaseating granulomatous inflammation. The differential diagnosis must exclude breast carcinoma and tuberculosis. A diagnosis of idiopathic granulomatous mastitis is made by excluding secondary causes, like tuberculosis.(12,14)

Treatment approach varies according to clinical findings. Small lesions may regress spontaneously, so monitoring may be sufficient in some patients. Antibiotic treatment can be applied in the same way as for periductal mastitis. Some studies suggest that steroid treatment may be beneficial in certain cases. Methotrexate can also be given along with steroids. In recurrent cases, and cases with abscess or fistula formation, surgery may be performed.(14,15)

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CHAPTER VI

GROWTH FACTORS IN THE TREATMENT OF DIABETIC FOOT ULCER

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1. İntroduction

Diabetes mellitus is a significant health issue as its incidence and financial burden have risen to concerning levels. The worldwide prevalence of diabetes was 451 million among the adult population in 2017 and is expected to affect 693 million people in 2045.(1) The global health cost of diabetes in 2019 was estimated to be around 760 billion US dollars and is estimated to increase to 845 billion US dollars by 2045.(2) Diabetic foot ulcers (DFU) develop as a combination of peripheral neuropathy and vasculopathy that leads to lower extremity infection, ulceration, and necrosis. It is estimated that 1 in every 4 diabetic patients will experience chronic foot injury sometime in their whole life.(3)

The recurrence rate of foot ulcers in a patient with a history of diabetic foot ulcers in the next 3 years is between 17-60%.(4) The standard management process consists of control of infection, wound debridement, and offloading therapy. Due to the disruption of wound healing mechanisms in diabetic patients, which is already a highly complex process, wound healing is compromised and further management modalities are needed in addition to the standard techniques. Growth factors are under investigation in order to understand the pathophysiology of the molecular mechanisms that are involved in the healing process in diabetic patients with foot ulcers and to evaluate the success of the treatment.

2. The Impact of Diabetes on Wound Healing

Wound healing is a complex process involving hemostasis, inflammation, proliferation, and remodeling. It also requires the activation of various cells like thrombocytes, fibroblasts, macrophages, myofibroblasts, smooth muscle cells, keratinocytes, and endothelial cells. Several growth factors released by these cells are necessary for the coordination and maintenance of healing. The wound healing process involves temporary matrix development by hemostasis, migration of neutrophils, monocytes, and epithelial cells, development of new blood vessels (angiogenesis), migration of fibroblasts to the wound site to produce granulation tissue, reepithelization of the wound surface, collagen deposition by remodeling of the matrix and development of scar tissue.(5,6) Any abnormality or disturbance in these processes may cause nonhealing wounds or pathological wound healing like hypertrophic scar or even keloid formation.(7) Wounds that last more than 4 weeks despite appropriate wound care is defined as a chronic wound.

Neuropathy and angiopathy provide the predisposing environment for diabetic foot ulcers. Many factors like decreased pain perception, predisposition to trauma, posture problems, dry skin, reduced sweating, foot deformities, and ischemia contribute to this process.(8) Hyperglycemia in diabetic patients disrupts most of the wound-healing processes. Neuropathy and hyperglycemia disrupt the leucocyte diapedeses, chemotaxis, and phagocytosis. Uncontrolled hyperglycemia causes neutrophil dysfunction, insufficient collagen synthesis, and increased production of inflammatory cytokines and consequently, the wound becomes chronic.(8) The healing process is prolonged in foot ulcers due to many factors like high levels of metalloproteinases, non-physiological inflammatory response, and inadequate levels of growth factors.(7) Extracellular matrix deposition may entrap inflammatory cells and create a predisposition for infection.(9) End products of advanced glycation secondary to hyperglycemia are proposed to have a significant contribution to oxidative stress and disrupted inflammation.(10) The phases of wound healing can not be synchronized in diabetic patients due to neuropathy, microangiopathy, and dysfunctional immunity.(11) To better understand the pathophysiology of ulcer healing in diabetic patients, the growth factors' role should be investigated extensively.

3. Growth Factors

Growth factors are responsible for communication between different cell types involved in wound healing and extracellular matrix. Deprivation of

growth factors causes disturbance in all phases of wound healing.(12,13) The main growth factors involved in wound healing include platelet-derived growth factor(PDGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF). Growth factors have an impact on various steps of wound healing like proliferation and migration of various cell types, endothelial cell stimulation, angiogenesis chemotaxis of fibroblasts and inflammatory cells, and production and reconfiguration of extracellular matrix.(7)

In a meta-analysis of 28 randomized clinical trials evaluating the effect of growth factors on the management of foot ulcers of diabetic patients, growth factors are shown to significantly improve healing compared to placebo and other management modalities. However, most of the studies were containing a significant risk of bias as pharmaceutical companies were financial supporters in 14 studies, and results were of low quality due to limitations and inconsistencies in the study design and conduction.(14) Growth factors are still under investigation for their possible impact on the altered signaling pathways of diabetic foot ulcers notorious for being resistant to treatment. Evidence-based, well-designed, and independent studies are still insufficient. Recommendations for the use of these products should be evaluated carefully.

Some of the common side effects of growth factors are pain, edema, infection, cellulitis, etc. However, reported side effects were not proven to be related to the drugs except for the dose-dependent side effects of vertigo and tremor.(15)

3.1. Platelet-Derived Growth Factors (PDGF)

PDGF is a dimeric protein contained by platelets, macrophages, fibroblasts, and endothelial cells.(16) It has a chemo-attracting and mitogenic effect on the fibroblasts, smooth muscle cells, and endothelial cells.(17) It stimulates the differentiation of the fibroblasts to the myofibroblasts and promotes the production of extracellular matrix components.(18) Furthermore, stimulates the production of other growth factors like vascular endothelial growth factor (VEGF) and transforming growth factor β (TGF- β).(18)

In the early 1990s, PDGF was shown to heal the diabetic wounds in diabetic rats.(19) Becapermin is a topically administered drug for diabetic foot ulcer treatment and approved by the FDA which is produced by recombinant DNA technology.(20) Recombinant human PDGF combined with standard wound care modalities are found to improve wound healing in diabetic foot ulcers and

tolerated well by the patients.(20) A meta-analysis of randomized controlled studies found that PDGF is effective in diabetic lower extremity wounds, and sensitivity analysis of the studies showed that they were credible without any publishing bias.(21)

Becaplermin gel is applied topically once a day with the help of a saline-soaked gauge. Risk/benefit analysis should be reevaluated if wound dimensions do not reduce by 30% in 10 weeks or complete healing does not occur in 20 weeks.(22) Due to carcinogenic potential, the maximum dose is limited to 3 tubes.(23)

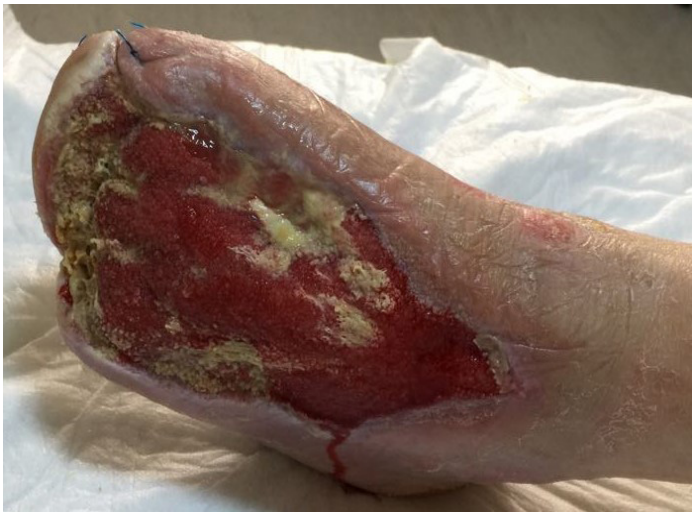
3.2. Fibroblast Growth Factor (FGF)

Fibroblasts are produced by chondrocytes, endothelial, smooth muscle, and mast cells. Fibroblast growth factor is one of the 23 members of the cell signaling protein family.(15) Disruptions in this cascade are related to impaired response to injury and disturbance in organogenesis, metabolic disorders, and developmental abnormalities that may lead to malignancy.(24) During epithelization, FGF increases keratinocyte migration and stimulates fibroblast proliferation and collagen production.[18] FGF is involved in embryonic development, angiogenesis, fibroblast proliferation, keratinocyte organization, and wound healing.(25) Trafermin, which is a recombinant human fibroblast growth factor has been used as a topical spray in Japan. It was related to faster recovery of burn wounds and reduced hypertrophic scar development.(26)

3.3. Epidermal Growth Factor (EGF)

Recombinant human epidermal growth factor (rhEGF) is a 53 amino acid-long polypeptide that was isolated in 1962 by Stanley Cohen and Rita Levi Montalcini from the submaxillary glands of rats by recombinant DNA technology. (27) It is produced by platelets, macrophages, monocytes, and fibroblasts. It stimulates the development of extracellular matrix, cellular reproduction, and angiogenesis and induces the reproduction of fibroblasts, keratinocytes, and vascular endothelial cells.(28) In patients with chronic diabetic foot ulcers, fibroblasts' response to EGF is blunted.(29) It is indicated in diabetic foot ulcers in the absence of infection (Figure 1). It can be used topically to the wound surface or available injectable forms can be injected to the wound bed or to the wound edges (Figure 2).

Figure 1: Prepared wound before intralesional EGF (Wound bed prepared before intralesional EGF with finger amputations, serial surgical debridement and negative pressure wound therapy to remove necrotic tissue



(From Serdar Gökay Terzioğlu's archive)

Figure2: Intralesional EGF application

(From Serdar Gökay Terzioğlu's archive)

Drug inefficiency due to necrotic tissue, sepsis, inflammation, and wound proteases is a major issue in topical applications. A meta-analysis of the topical and intralesional applications concluded that topical application is recommended in Wagner 1-2 ulcers and intralesion application is recommended in deep ulcers.(30)

Epidermal growth factors are shown to improve wound healing and reduce amputation rates in grade III-IV ulcers.(31,32) A dose comparison study revealed that a 75 µg EGF regimen provided higher healing rates and shorter recovery durations than a 25 µg EGF regimen.(33) Topically applied recombinant human (rh)-EGF and PDGF were also found to improve wound healing and stated that rhEGF may be the best growth factor available.(34) In selected patients, EGF application into the lesions is an effective complementary treatment modality. In our country and other developing countries, high cost restricts its widespread utilization.

The intralesional EGF treatment regimen consists of an 8-12 weeks protocol of 75µg/day EGF applied into the wound bed and wound margins 3 times a week. Side effects include pain, burning sensation, tremors, sweating, and nausea. To reduce the incidence of side effects, antihistaminic medication and acetaminophen are recommended.(35)

3.4. Vascular Endothelial Growth Factor (VEGF)

VEGF is an important chemokine that plays a critical role in angiogenesis and vasculogenesis.(13) It promotes collagen deposition and epithelization in wound healing.(36) Hypoxia is a significant stimulator of VEGF release. Therapeutic use is supported for vascular restoration in the ischemic tissues and wounds. It also plays a role in the regulation of vascular development and morphogenesis, vascular permeability, and chemotaxis of the endothelial and inflammatory cells.(37)

In rabbits, VEGF is shown to increase granulation tissue in dermal wounds but no effect on the epithelization is found.(38) An animal model of diabetic rats supported the use of VEGF to increase tissue repair in acute and chronic injuries to support the tissue repair.(39) There are ongoing gene therapy studies that aim to increase the potency of the VEGF.(40)

5. Conclusion

Despite the encouraging results of the growth factors on wound healing in animal studies, there are few well designed studies. The International

Working Group for Diabetic Foot (IWGDF) stands against the use of topical growth factors in challenging DFUs as evidence regarding the cost-effectiveness analysis of growth factors is insufficient.(41) In Türkiye, the epidermal growth factor is available in gel and injectable forms. It is indicated in diabetic foot ulcers without gangrene and without infection. The high cost of growth factors is a self-limiting factor against widespread utilization in our country.

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CHAPTER VII

SURGERY IN TUBERCULOSIS

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1. Introduction

Thoracic surgery has a long history intertwined with tuberculosis (TB) management. It dates back to ancient Greece, with Hippocrates describing early chest surgery for TB. Modern thoracic surgery emerged after the discovery of Mycobacterium tuberculosis. Surgical techniques were developed in the late 19th and early 20th centuries to combat TB, and many foundational surgical approaches were established during this time. (1)

The advent of effective TB drug therapy led to a decline in surgical TB treatment. Thoracic surgery was revitalized by the rise in lung cancer cases in the later part of the 20th century. Recently, there has been renewed interest in thoracic surgery for TB due to factors like increased TB incidence, drug-resistant TB, and non-TB mycobacteria infections. Modern thoracic surgery offers effective TB management with reduced pain and morbidity, and minimally invasive techniques have expanded surgical options for TB patients. (2)

2. Surgery for Diagnosis of Tuberculosis

One of the initial hurdles in TB management involves its accurate diagnosis. The paucibacillary nature of Mycobacterium TB infection often poses challenges in confirming the disease through traditional microbiological methods, such as culturing sputum samples, bronchial aspirates, and especially pleural fluid. (3) In cases where patients exhibit clinical symptoms and radiological findings indicative of TB, but conventional diagnostic approaches yield inconclusive

results, surgical biopsy may serve as a valuable tool to definitively confirm the diagnosis in specific individuals. (4)

Identifying an appropriate biopsy target is paramount, usually facilitated by a thoracic CT scan which frequently identifies potential biopsy sites, including the lung parenchyma, mediastinal lymphadenopathy, and pleura. The choice of biopsy site mainly hinges on the probability of obtaining a positive result, determined by the volume and accessibility of the affected tissue visualized on the CT scan. (5, 6)

Other critical considerations encompass the patient's capacity to withstand one-lung ventilation and prolonged anesthesia. Moreover, potential impediments to specific surgical techniques, such as an extant tracheostomy obstructing mediastinoscopy or anticipated dense adhesions from previous surgeries, warrant attention. Given these intricacies, it is vital to employ a multidisciplinary approach, integrating expertise from respiratory physicians, thoracic surgeons, radiologists, and anesthetists. This cohesive team collaboratively determines an optimal biopsy target and evaluates surgical risks. For patients where surgery presents considerable risks, alternative diagnostic avenues or even empirical anti-TB treatments might be explored. (7, 8)

2.1. Lung Parenchyma

Radiological imaging, including advanced methods like CT and positron emission tomography, cannot definitively diagnose TB in the lung parenchyma. The success rate of percutaneous imaging-guided biopsy is variable, and it has been reported that the positive diagnosis rate ranges from 20% to 80%. (9) On the other hand, fiber-optic bronchoscopy methods can only diagnose smear-negative TB in 30% to 58% of cases, making surgical lung biopsy still necessary for some patients. (10)

When considering a biopsy, the ideal target is a distinct mass or opacity on CT located near a lung lobe edge or interlobar fissure. This allows for a small wedge of lung tissue to be removed, minimizing respiratory impact. If no specific target is found, a wedge can be taken from an area with the most noticeable change. In cases of bilateral disease, some surgeons prefer the right lung due to its extra fissure and lobe edges. Deep lesions far from a lobe edge pose technical challenges. Extremely deep lesions might require significant resections, while smaller, deep lesions might be hard to locate during surgery. For such hard-to-locate lesions, a hook wire placed by an interventional radiologist can help in detection. (11-13)

Surgical principles for lung biopsy involve either open thoracotomy or more commonly, video-assisted thoracoscopic surgery (VATS). (10) The biopsy method typically involves excising a wedge of tissue, often using a surgical staple-resection device. VATS offers a high diagnostic accuracy rate of 90% to 95% and allows most patients to be discharged the day after surgery. (14) Given its efficiency and minimal impact, VATS is emerging as a preferred alternative to other diagnostic methods in selected patients.

2.2. Pleural Effusion

When TB presents as a pleural effusion, diagnosing it isn't straightforward. The typical method, percutaneous biopsy of the parietal pleura, lacks precision, achieving a positive diagnosis in only 54-82% of cases. (15) Even with the aid of ultrasound, the accuracy only slightly increases. In situations where these methods are inconclusive, surgical exploration becomes the go-to approach. A significant advantage of this surgical route is the ability to immediately address advanced stages of empyema thoracis if detected. (16)

The procedure for pleural biopsy mirrors that of lung biopsy. While the traditional open thoracotomy remains an option, the trend leans towards the less invasive VATS. VATS provides enhanced visualization, making it a preferred choice for many. The process involves draining any pleural fluid and meticulously inspecting the pleura to pinpoint biopsy sites. Over the years, VATS has earned its reputation as a reliable method, boasting a diagnostic success rate of up to 100%. Recovery is swift, with most patients heading home within a couple of days. (17)

An emerging alternative to VATS is the more traditional "medical" thoracoscopy, performed under local anesthesia. This procedure, which is essentially the precursor to modern VATS, involves a single incision and the insertion of a thoracoscope into the pleural space. Its main appeal is the avoidance of general anesthesia, positioning it as a potential day-case procedure. However, it's not without its challenges, including potential discomfort for the patient. As of now, the full potential and role of thoracoscopy in TB diagnosis remain under exploration. (18, 19)

2.3. Mediastinal Lymphadenopathy

In TB patients, sometimes the only detectable signs for biopsy are enlarged intrathoracic lymph nodes. Distinguishing between hilar nodes and mediastinal nodes is crucial. (20) Hilar nodes, accessible only via thoracotomy or VATS, are

often associated with postinflammatory adhesions, making biopsy technically challenging. Mediastinal nodes, on the other hand, are more accessible and can be approached in various ways, including transbronchially. One of the least invasive methods for biopsy of certain nodal stations is transbronchial needle aspiration (TBNA) via fiber-optic bronchoscopy. The recent advancement, endobronchial ultrasonography (EBUS), enhances TBNA by providing detailed imaging of lymph nodes. However, its role in TB diagnosis is still being explored. (21, 22).

Traditional surgical approaches include cervical mediastinoscopy, which accesses paratracheal lymph nodes in the mediastinum. This method is often preferred over VATS when only specific nodal stations need to be examined, as it doesn't require one-lung ventilation. Another older method, anterior mediastinotomy, targets nodes unreachable by standard cervical mediastinoscopy but has been largely replaced by VATS. VATS, whether through a 3-port or uniportal approach, provides comprehensive access to various nodal stations, offering a larger tissue sample than other methods. However, it usually targets lesions on one side of the chest per session. (23, 24)

3. Indication and Contraindications for Pulmonary Tuberculosis Surgery

Cavitary multidrug-resistant (MDR) / drug-resistant (XDR)-TB that doesn't respond to anti-TB chemotherapy is currently seen as the primary reason for surgical treatment, which is then followed by post-operative anti-TB chemotherapy. Studies have shown that individuals who underwent surgery had a success rate of 92% in the short term and 87% in the long term. When comparing surgical and non-surgical treatments, a systematic review of various studies indicated that surgical patients generally had a higher treatment success rate. (25) Specifically, two meta-analysis studies found that surgical patients had success rates of 69% and 81.9%, while non-surgical patients had rates of 60% and 59.7%. (26, 27) Notably, patients who underwent partial lung resection had better outcomes than those who had a pneumonectomy or no surgery at all. (25) Indications for pulmonary TB surgical intervention include (28):

• Persistent or intermittent positive sputum bacteriological results after standard anti-TB therapy, with localized lung lesions.

• Despite negative sputum bacteriological findings, the presence of irreversible lung alterations such as tuberculous cavities, lung damage,

atelectasis, or pronounced bullae. Removing non-functional lung tissue can enhance respiratory function and optimize the ventilation-perfusion balance.

• Even if TB is resolved or partially addressed, complications like bronchiectasis, repeated hemoptysis, tuberculous empyema, or malignancies might be present.

• A crucial prerequisite for PTB surgery is the bacteria's sensitivity to at least two anti-TB medications. While surgery can extract infected tissue, it doesn't eradicate all TB bacteria. Hence, post-surgical anti-TB therapy is vital. If the bacteria aren't sensitive to a minimum of two anti-TB drugs, sole reliance on surgery can be perilous. Surgery might be an option for MDR-TB and XDR-TB patients unresponsive to anti-TB chemotherapy, given certain conditions. It's pivotal to consider surgery before the bacteria evolve into MDR or XDR stages due to the notably lower success rates.

• Ensuring patients are well-informed and accepting of the surgical risks and treatment plan is essential. The extent of TB, whether limited to a single lobe or spread across the lung, doesn't necessarily influence surgical outcomes.

Contraindications include (28):

• Individuals with compromised cardiopulmonary capabilities unsuitable for surgical procedures.

• Presence of active TB in the remaining lung or the opposite lung post-surgery.

• Active bronchial TB located at the site intended for lobe resection.

• Bacterial strains in the patient showing complete resistance to both primary and secondary anti-TB medications.

• Patient's unwillingness or refusal to undergo surgery.

4. Methods of Pulmonary Tuberculosis Surgery

TB surgery primarily employs two methods: collapse therapy and direct lesion removal. Collapse therapy aims to induce lung and chest collapse by rib removal, altering the thoracic shape to encourage cavity closure. However, its effects are temporary, and it can lead to noticeable postoperative thoracic deformations. Consequently, many patients prefer lesion removal. Lesion removal varies based on the lesion's size and affected lung area (1, 2, 28-30):

• **Wedge Resection:** Suitable for localized peripheral pulmonary lesions, often used for biopsy in ambiguous cases resembling lung cancer. This procedure can be performed through minimally invasive thoracoscopic surgery.

• **Segmentectomy:** Commonly used for TB treatment, especially for specific lung segments. The procedure requires careful separation along the lung segment without suturing the segment surface. Its advantage is minimal lung tissue removal, preserving lung function. However, few patients have lesions restricted to a single segment.

• **Lobectomy:** Often the preferred surgical treatment for PTB, especially for cavitary TB concentrated in the upper lobe. It's suitable for a limited number of cases, as TB typically affects more extensive lung areas.

• **Pneumonectomy:** Used for severe TB cases, including drug-resistant strains. It involves removing an entire non-functioning lung, providing immediate benefits like increased blood oxygen saturation. However, long-term consequences, like pulmonary hypertension, may arise.

• **Compound Removal:** Necessary when TB affects adjacent lung tissues, ensuring comprehensive lesion clearance.

TB surgeries are more challenging than those for lung cancer due to the extensive pleural adhesions from prolonged TB inflammation. This often results in bleeding during adhesion separation. Moreover, TB patients frequently have inflamed hilar lymph nodes, complicating the separation process. Hence, thoracoscopic surgery, though widely used, is challenging for TB, especially for MDR-TB patients. Traditional thoracotomy remains the recommended approach for many TB surgeries. (29, 30)

5. Postoperative Treatment and Prognosis

Several studies on tuberculosis surgery have discussed the use of "standard" anti-tuberculosis treatment post-resection. However, the primary concern of these studies was the reliability of the surgical method, not the long-term outcomes post-surgery. (31,32) The practice of using standard anti-tuberculosis treatment after surgery isn't strongly backed by evidence-based medicine. This approach has its roots in the surgical treatment of earlier active tuberculosis cases, such as those with drug-resistant or cavitary tuberculosis. Currently, the World Health Organization's (WHO) criteria for clinically curing tuberculosis include continuous negative sputum results, significant lesion improvement or absorption, and cavity closure or reduction lasting more than six months. (33)

After surgery, it has been reported that 29-50% of patients experience complications such as secondary respiratory insufficiency, infection in other

areas, chest bleeding, and heart failure. After surgery, patients may develop physical and mental sensitivities, leading them to refuse medication or harbor fears about taking drugs. This can complicate the patient's adherence to the treatment. (34, 35)

It is advised to perform surgical resection on infectious TB patients after a minimum of 6–8 months of suitable anti-TB treatment (10, 33). A recent comprehensive study indicated an 84% success rate in treating MDR /XDR-TB patients through pulmonary resection, accompanied by a 6% failure rate, 3% recurrence, and 5% death rate. (36)

6. Conclusion

Historically, thoracic surgery and TB treatment have shared a deep connection, tracing back to early medical practices. As modern medicine evolved, the role of surgery in TB management witnessed shifts, with the advent of effective TB drugs reducing its prominence. However, the rise of challenges like drug-resistant TB has reignited interest in surgical solutions. Diagnosing TB accurately often necessitates surgical biopsies, given the limitations of traditional methods. Various surgical techniques, from wedge resection to pneumonectomy, are tailored based on the disease's location and severity. Modern techniques have transformed thoracic surgery, ensuring not only effective TB management but also minimizing patient trauma and complications. The rise of minimally invasive procedures broadens the spectrum of TB patients who can benefit from surgical solutions, emphasizing its growing significance in comprehensive TB care.

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CHAPTER VIII

ULTRASOUND-GUIDED PERIPHERAL NERVE BLOCK APPLICATIONS IN CHRONIC PAIN MANAGEMENT

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1. Introduction

The International Association for the Study of Pain (IASP) classifies chronic post-surgical pain (CPSP) as a secondary chronic pain condition in the WHO International Classification of Diseases (ICD-11). (1) CPSP is defined as chronic pain that develops or increases in intensity after a surgical procedure or a tissue injury and persists beyond the healing process, i.e. at least 3 months after the surgery or tissue trauma. The new definition brings some uniformity and clarity in reporting the incidence of CPSP after various surgical procedures. The cumulative overall incidence varies from as low as 5% to as high as 85%. Thoracotomy, sternotomy, mastectomy, cholecystectomy, inguinal hernia repair, and limb amputation are a few of the surgical procedures known to have a high incidence (ranging above 50%). (2)

As our population ages, the number of surgeries performed each year has increased both in absolute terms and per capita. (3) With these surgeries becoming increasingly complex, largely as a result of advancing anesthesia techniques, morbidity and mortality have continued to decrease. These facts have led to a greater emphasis on improving secondary outcome measures such as functional capacity and psychological well-being. Perhaps most notably, this emphasis is seen in efforts to prevent and treat CPSP.

While most patients undergoing surgery recover smoothly and return to their normal lives within a few weeks, a significant number develop debilitating

chronic pain that can affect their occupational, social, and psychological health. Similar to the treatment of other pain conditions, a multimodal approach is described here, which identifies patients at risk of CPSP, takes rational preventive measures, minimizes iatrogenic trauma, uses aggressive postoperative analgesic techniques, and addresses concomitant psychopathology that can exacerbate or even accelerate neuropathic pain. It assumes that post-procedure monitoring, an often underappreciated aspect, is mandatory to control this evolving problem.

2.1. Definition

The definition of CPSP is problematic. Based on definitions of chronic pain, it can logically be defined as pain lasting longer than the expected natural healing course after surgery or pain persisting for more than 3 months after surgery. (4) Currently, there is no universally accepted single definition for CPSP, and debates exist about whether universally accepted standard reference criteria are possible. Therefore, the diagnosis is generally one of exclusion. First, the recurrence of the initial surgical pathology (such as recurrent hernia in the groin or abdomen) should be ruled out, followed by the exclusion of a new pathological condition (e.g., pneumothorax). The nature and character of the pain may also help raise suspicion that the pain generator is of low likelihood of visceral or somatic origin.

In 1999, Macrae proposed a definition for CPSP based on four criteria: (1) development after a surgical procedure; (2) duration ≥2 months; (3) exclusion of other causes; and (4) an attempt to explore and exclude the possibility that the pain arises from a pre-existing problem. (5) However, this definition itself is inherently fraught with dilemmas. For many surgical procedures associated with high prevalence rates of CPSP, such as inguinal hernia repair and laminectomy/spinal arthrodesis, pain is one of the primary indications for intervention. In many patients who undergo spinal decompression, gallbladder removal, or hernia repair, minimal or uncertain pathologies are observed, making it extremely difficult to distinguish between pre-existing conditions and iatrogenic pain.

2.2. Clinical Presentation

The clinical characteristics of post-surgical pain are often a function of the type of surgery performed. Regardless of the underlying cause, many patients use typical neuropathic pain descriptors such as “shooting,” “burning,” and “stabbing” to describe their symptoms. Pain is typically localized to the area where the surgery was performed or around the surgical incision. Patients may

complain of associated symptoms, such as dysuria or testicular pain after hernia repair, pleuritic pain after thoracotomy, radiation to the arm on the same side after mastectomy, and phantom sensations following limb amputation.

2.3. Epidemiology

The prevalence rate of CPSP is likely influenced by many factors, but a better understanding of the precise role each plays in the pathogenesis is needed. Because many of the factors influencing the development of CPSP are dynamic (e.g., demographic characteristics of surgical patients, the spectrum of surgeries), changes in incidence should be expected to occur together. (6) In addition to changing demographic and clinical factors, the method and frequency of surveillance can affect CPSP estimates. (7) For example, initial rough estimates of the frequency of phantom limb pain routinely fell below 5%, but more recent and refined measurements have measured its occurrence between 50% and 80%. (8)

Table 1. Factors Influencing Incidence of CPSP

Genetic
Younger age
Female
Opioid-induced hyperalgesia
Intensity and duration of pain
Presence of concomitant pain disorders
Education level
Psychosocial factors
Anesthetic protocol
Surgical trauma
Type and technique of surgery (e.g., laparoscopic and open)

However, many researchers have attempted to determine the scope of CPSP. Perhaps due to variability in definitions and surveillance methods, these estimates range widely from less than 0.5% to as high as 10%. (9) In a prospective study, Hayes et al. and Visser estimated the prevalence of neuropathic pain one year after surgery to be between 0.5% and 1.5%; this was later confirmed in an epidemiological review by Visser. (10) Surgery is a contributing factor

in approximately 20% of cases among patients seeking medical help in pain management clinics. (11)

3. Rısk Factors

In recent years, there has been significant research into identifying predictive factors for CPSP following various surgical procedures. These studies have uncovered several risk factors spanning the surgical process, from preoperative to intraoperative and postoperative phases. (12,13) CPSP often exhibits neuropathic characteristics and, like most neuropathic pain conditions, presents a therapeutic challenge. Hence, it is crucial to understand these risk factors and develop preventive strategies.

Numerous potential risk factors have been linked to an increased likelihood of developing chronic pain. These factors include the duration of surgery, the use of low-volume surgical units, the choice of an open or endoscopic approach, the use of pericostal or intercostal sutures, traditional hernia repair techniques, and the possibility of intraoperative nerve injury. (14) While there is no conclusive evidence establishing a direct causal relationship between these factors and CPSP, a common element among them is the presence of significant surgical trauma and the potential for intraoperative nerve damage. Acute nerve injury is believed to trigger changes in the injured nerves, adjacent nerves, and the central nervous system. Evidence from animal studies indicates that peripheral nerve damage leads to prolonged, high-frequency bursts of nerve activity. This heightened activity sensitizes nociceptive pathways, involving N-methyl-D-aspartate receptors in the central nervous system. (15)

For instance, in a rat model of post-laparotomy pain involving a subcostal incision to access the peritoneal cavity, a 50% reduction in locomotor activity was observed within 24 hours after surgery. The subsequent restoration of normal locomotor activity with the administration of morphine and ketorolac suggests that behavioral aspects are similar to those seen in postoperative pain. (16)

3.1. Preoperative and Host-Related Factors

A consistent factor related to patients with CPSP is the presence of preoperative pain, either as the indication for surgery or in an unrelated area. In a study examining the presence of CPSP after hysterectomy, a prevalence of 31.9%

was observed one year after surgery. Risk factors identified through multiple logistic regression included preoperative pelvic pain, pain that was the indication for surgery, previous cesarean section, and other preexisting pain problems. A subsequent prospective study in patients who underwent hysterectomy also revealed that preoperative pain problems in other areas were associated with pain that developed four months after hysterectomy. (17) A similar trend was observed, although not statistically significant, for preoperative pelvic pain.

3.1.1. Psychological Factors

Several psychosocial determinants have been identified in the development of CPSP and/or disability. (18) These include characteristics such as surgery-related fear, heightened preoperative anxiety, introverted personality, catastrophizing, and psychic vulnerability. The impact of preoperative psychological distress and somatic preoccupation on predicting persistent pain following reconstructive surgery after mastectomy was examined in a prospective study of 295 women. Abdominal and back pain were significantly associated with emotional distress, depressive and anxiety symptoms, and somatization. These psychological measures also predicted more severe breast pain one year after reconstructive surgery. (19)

3.1.2. Genetic Factors

Studies in experimental animals and human twins suggest that genetic factors play a role in the risk of developing chronic pain. Screening of hundreds of genes regulated in dorsal root ganglia following peripheral nerve injury led to the identification of the guanosine triphosphate cyclohydrolase 1 (GCH1) gene. The GCH1 enzyme catalyzes tetrahydrobiopterin (BH4), a cofactor necessary for the production of various mediators (e.g., catecholamines, serotonin, and nitric oxide) increased in peripheral inflammation and injury. In humans, GCH1 (population frequency 15.4%) has been associated with a lower prevalence of persistent radicular pain after surgical discectomy. Other genes with identified polymorphisms have also been shown to be associated with chronic pain. These include genes coding for a serotonin transporter, 5-HTTLPR, and the catechol-O-methyltransferase (COMT) enzyme, which inactivates dopamine, epinephrine, and norepinephrine in the nervous system. One future goal is to genotype a "pain genes" panel for patients undergoing surgery to accurately predict their risk of postoperative pain and response to various analgesics. (20)

3.2. Surgical and Intraoperative Factors

A retrospective study involving 243 patients who underwent video-assisted thoracoscopy or thoracotomy revealed that younger age, radiotherapy, pleurectomy, and more extensive surgery predicted CPSP. Another study in patients post-mastectomy suggested that the surgical site might be a potential risk factor for chronic pain. Women who had undergone right-sided mastectomy were more likely to report existing breast pain, experience phantom breast pain, and describe themselves as disabled. Sequelae related to pain (e.g., disability at work) were more common after right-sided mastectomy. It is unclear whether other types of surgery exhibit a similar laterality effect. (21)

3.2.1. Anesthetic Management

An epidemiological study examining risk factors for persistent pain after hysterectomy and spinal anesthesia found that anesthesia was associated with a reduced risk of chronic pain one year after surgery. It is suggested that a more complete blockade of central stimulus traffic in spinal anesthesia may have a protective effect against the development of chronic pain. (22)

3.3. Postoperative Factors

A reliable indicator of persistent postoperative pain is the intensity of early postoperative pain. In the case of lateral incisions for thoracotomy, the primary predictor of chronic pain 18 months after surgery was the intensity of pain at rest and during movement 24 hours after surgery. (23) A prospective study conducted on hysterectomy patients also revealed an association with high acute postoperative pain intensity and the emergence of pain four months after the procedure. (24) Comparative studies of different conditions have shown that analgesic strategies during the postoperative period, interventions that reduce postoperative pain, and interventions that reduce the area of hyperalgesia surrounding the wound are all associated with a decrease in CPSP. (25)

3.3.1. Post-Traumatic Stress Disorder

Recent studies have shown that post-traumatic stress symptoms are associated with CPSP months or even years after the traumatic event. Katz and Seltzer investigated the prospective relationship between post-traumatic stress symptoms and CPSP in patients who underwent thoracotomy. (26) They observed occurrence rates of 68.1% and 61.1% at 6 and 12 months of follow-up,

respectively. While avoidance symptoms were not significant, emotional numbing contributed significantly to the explanation of pain disability at both follow-up time points. The mechanisms underlying these relationships have not yet been determined.

4. Prevention

Intuitively, the minimally invasive techniques seem to reduce the incidence of CPSP. Studies suggest that multimodal analgesia, which combines multiple pain relief methods, can provide more effective analgesia than any single method, reduce the frequency of adverse effects, and result in a lower incidence of CPSP. For example, a single dose of 1200 mg of gabapentin administered one hour before mastectomy has been shown to reduce opioid consumption and pain scores. (27,28)

Free radical scavengers such as vitamin C, N-acetylcysteine (NAC), and mannitol are thought to be neuroprotective against excitotoxic insults. The use of vitamin C initiated two days before surgery and continued for 50 days at a daily dose of 500 mg has been suggested to reduce the frequency of complex regional pain syndrome (CRPS) after wrist arthroplasty. (29) However, in a recent study involving 41 CRPS patients who were administered mannitol, it was concluded that intravenous 10% mannitol was no more effective than a placebo in reducing CRPS symptoms. (30)

Improving the determination of surgical necessity can be effective in preventing CPSP. In a study evaluating preoperative and postoperative pain in inguinal hernia surgery, it was observed that patients without preoperative pain experienced significant pain after surgery. (31) Preoperative pain tends to improve following surgical interventions. Careful observation without immediate surgical intervention has been shown to be safe in asymptomatic inguinal hernia patients. Previous studies have generally indicated a correlation between emotional distress and greater acute pain. (32) Therefore, particularly in oncological surgery, considering the emotional well-being of CPSP patients and employing stress-reducing techniques can be effective in preventing CPSP.

In contemporary medical practice, various drugs and techniques are employed for postoperative pain control. Preemptive analgesia is defined as anti-nociceptive treatment that prevents changes in central processing of afferent input, which would otherwise enhance postoperative hyperalgesia and allodynia. Preemptive analgesia is believed to reduce altered central sensory processing by decreasing the incidence of postoperative hyperalgesia and allodynia.

Preemptive analgesia has expanded towards protective analgesia. While the timing of protective analgesia is not mandatory, incisional analgesia can block the stress response. Adequate protective analgesia should encompass various drugs along with multimodal techniques to reduce both peripheral and central sensitization. McCartney et al. reported that systemic administration of N-methyl-D-aspartate (NMDA) receptor antagonists like ketamine or dextromethorphan provided preemptive analgesic effects but did not observe any positive effect. (33,34) Lavand'homme et al. showed a combination of epidural analgesia and systemic ketamine administration to reduce the area of hyperalgesia around the surgical incision and impact delayed pain in patients undergoing colectomy. (35) Despite discrepancies among recent clinical studies, it's not only the timing of analgesia management but also the duration and efficacy of analgesic interventions that are crucial in the treatment of pain and postoperative hyperalgesia. (36)

5. Treatment

There is no standardized treatment algorithm for managing CPSP. CPSP commonly presents as neuropathic pain, and thus, the majority of treatment approaches involve pharmacological neuromodulators. These include anticonvulsants, antidepressants, opioids, and, as a last resort, neuromodulation techniques if conservative treatments prove ineffective.

O'Connor and Dworkin have recently issued consensus treatment guidelines for neuropathic pain within the framework of the International Association for the Study of Pain's Neuropathic Pain Special Interest Group (NeuPSIG). Grounded in randomized controlled trials, their recommendations for first-line treatments encompass antidepressant medications such as tricyclic antidepressants and dual reuptake inhibitors affecting both serotonin and norepinephrine, calcium channel alpha-2-delta ligands like gabapentin and pregabalin, and topical lidocaine. Second-line options include opioid analgesics and tramadol. It is worth noting that second-line treatments can be employed as first-line choices in specific clinical scenarios that demand immediate relief for acute neuropathic pain, while maintaining a plan to transition to the suggested first-line agent. Third-line alternatives, intended for refractory cases, encompass additional antidepressants and anticonvulsants, including topical capsaicin, mexiletine, and NMDA receptor antagonists, among others. (37)

CPSP treatment requires a personalized approach and may vary for each patient. The treatment plan should be determined based on factors such

as the severity and duration of pain, the patient's overall health, and other individual factors. Therefore, it's important to work with a pain specialist or a multidisciplinary pain management team for the treatment of CPSP.

Interventional treatment methods may be particularly useful for post-amputation and post-thoracotomy pain. Epidural analgesia, intercostal, ilioinguinal, and genito-femoral nerve blocks may be administered to address phantom limb pain, post-thoracotomy, and post-hernia repair pain. If pharmacological treatment and nerve blocks fail to provide benefit, pulsed radiofrequency and spinal cord stimulation of the dorsal root ganglion are increasingly recognized as treatment modalities in selected patients including neuropathic pain. Pulsed radiofrequency of the dorsal root ganglion has a superior effect than pharmacotherapy or pulsed radiofrequency of the intercostal nerves in the treatment of CPSP. (38)

Innovative treatment methods have been developed to address challenging CPSP. One of these is called mirror visual feedback therapy for the treatment of phantom limb pain. Mirror visual feedback therapy involves the use of a mirror placed vertically in the sagittal plane; the amputated limb is placed behind the non-reflective side of the mirror, and the intact limb is placed opposite the reflected side. The person is then asked to move the intact limb, in which case the intact limb is reflected as a mirror image that obeys the motor commands of the amputated limb; the person receives a visual impression of the amputated limb moving in accordance with motor commands sent to both limbs. Since Ramachandran et al's early report on the use of mirror therapy for phantom limb pain, other researchers have replicated this study and evaluated the effectiveness of mirror visual feedback therapy on primary outcome measures such as reduction in activity-related visual analog pain scores and motor function assessed with the Wolf motor function test. (39,40)

6. Summary

CPSP lacks clear and universally accepted definitions in the medical literature. This absence of a standardized operational definition poses challenges for epidemiological and clinical research, as well as for making meaningful cross-comparisons. Nevertheless, it has been reported that CPSP can affect up to 10% of patients who undergo surgery. The type, extent, and duration of the surgical procedure are influential factors that affect the risk of experiencing postoperative pain. As things stand, the most reliable preventive measure for CPSP is to minimize the need for surgery whenever possible. However, in cases

where surgery is medically necessary, it is crucial to maintain a high level of suspicion if postoperative pain persists for more than 2-3 months.

Current research efforts are directed toward creating a predictive risk index that amalgamates preoperative, intraoperative, and postoperative factors. This index aims to assist in the identification of patients at a heightened risk of developing persistent postoperative pain. The early implementation of a neuropathic treatment regimen, encompassing interventions such as nerve blocks, epidural injections, and spinal cord stimulation, offers the best prospects for a successful outcome. Additionally, innovative, non-invasive treatment methods like mirror visual feedback therapy are being explored as valuable tools in managing challenging forms of CPSP, such as phantom limb pain.

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