Prophylactic Surgery

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Editors

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Foreword

The best chance to cure cancer is to remove the tissue at risk before malignant transformation, and this concept extends to abnormal tissue that may ultimately require radical surgical resection. This comprehensive and timely text, and the first, addresses the increasingly recognized and accepted role of surgical resection to prevent cancer mortality and long-term morbidity of dysfunctional tissue. Genetic testing for personalized medicine has progressed rapidly and includes single-gene testing, panel testing, genome sequencing, and chromosomal microarrays. Perhaps the best known example is prophylactic mastectomy for breast cancer, the so-called Angelina Jolie effect. The decision to proceed with prophylactic surgery requires knowledge and skills of the surgeon and courage on behalf of the patient.

The editors author the first three chapters that provide compelling rationale for prophylactic surgery and emphasize the benefits to the individual patient as well as society in general. The patient has improved chances for survival and importantly reduced morbidity due to the opportunities to perform many of these operative procedures with minimally invasive techniques. Timely surgery also avoids chemotherapy, radiation, and immunotherapy. While there has been remarkable improvement in survival for many malignancies, the obligatory multimodal therapy and imaging to assess responses is costly.

Consequently, this text should be of great interest to surgeons, primary care physicians, patients and their family members, and health-care policy makers.

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Preface

Dear Readers,

Prophylactic surgery can be defined as procedures to partially or completely remove organs or tissues that may appear normal or functional now, but are likely to transform into significant pathologies such as malignancies or other diseases in future.

Such transformation is multifactorial; environmental and genetic factors play an important role. Various measures can be taken to mitigate these two etiological factors in order to prevent the development of life- or quality of life-threatening diseases. Prophylactic surgery has started to be applied increasingly in recent years as a preventive procedure, especially in cases where genetic transition features are revealed. In this respect, breast, colon, stomach, thyroid, and ovarian cancer syndromes are known classic examples.

In this book, the conditions and organ-specific applications that require prophylactic surgery for the elimination or prevention of pathologies that occur primarily for genetic and environmental reasons are examined in the light of current literature. In addition to the applications in the General Surgery subdisciplines, chapters from related branch authors have been added to give an idea of other surgical branch applications.

The aim of the book is to reveal the potential, limits, and applicability of prophylactic surgery in a number of conditions and clinical situation. Some risk-reducing procedures, applied in different disciplines in many symptomatic or asymptomatic cases, are also discussed.

It is understood that prophylactic surgery will become a discipline of its own in the very near future. In this book, we believe that physicians from every branch can find a topic of relevance to their own work.

Sixty-nine authors from 31 different institutions in 10 countries contributed to the preparation of the book. We would like to thank each individual contributor to this book for their valuable input and all authors for sharing their vast experience through their contributions. In addition, we would like to thank Donatella Rizza and Aruna R Sharma from the Springer Nature team for their kind collaboration and support in realizing this unique project.

Our hope/aim is that *Prophylactic Surgery*, which is the first book in its field, will give the reader a different view and approach style to this emerging and exciting prospective field.

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Prophylactic Surgery: Why, When, and How?

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Osman Nuri Dilek

1.1 Prophylactic Surgery

1.1.1 Introduction

Prophylactic surgery (PS), also called preventive surgery, early surgery, preemptive surgery, or risk-reducing surgery, involves partial or complete removal of organs or body tissues that may appear healthy now, but are likely to become ill due to cancer or other causes in the future. PS has been defined as risk-reducing procedures by the American Society of Clinical Oncology (ASCO) and the Society of Surgical Oncology (SSO) [1]. In the NIH-NCI dictionary of cancer terms, PS is defined as "surgery performed to remove an organ or gland that does not show signs of cancer in order to prevent the development of cancer of that organ or gland" [2].

Environmental and genetic factors play an important role in cancer development. There are germline mutations in hereditary transitions and the risk of developing cancer increases. For example, BRCA1/2 positive women have a 5–40-fold increase in cancer development risk [3]. Besides, mutations can occur in some of the germ cells in the early stages of the organism's development and cause mosaicism in the gene line. Anatomical and functional problems arise after birth, depending on the location of the gene damage caused by mosaicism. Somatic mutations that play a role in forming sporadic cancers are known to develop spontaneously or due to external (environmental) factors as a natural consequence of aging [4]. For example, in the background of gastroesophageal reflux, Barrett's esophagus and the risk of developing cancer increase 30 to 40 times [5].

Prophylactic surgery's application area is genetically transmitted cancers, precancerous lesions, and asymptomatic noncancerous pathologies that can threaten life and function with its complications (Table 1.1). Prophylactic appendectomy and cholecystectomies can also be performed to minimize complications during space travels or prolonged polar voyages and to avoid risking the lives of passengers and crew [6].

Prophylactic surgery has been increasingly used in recent years as a preventive procedure, especially in genetic predisposition cases. In this respect, colon, breast, stomach, thyroid, and ovarian cancer syndromes are classic examples. Much data in the literature on surgical methods to be applied, especially inherited diseases involving the breast and colon. Algorithms containing organ-specific diagnosis and treatment approaches have been developed. Besides, with the advances in imaging and other diagnostic tools, many nonhereditary diseases can be detected in the "in situ" or "high-grade dysplasia" stage, and they have begun to be treated with prophylactic organ/tissue resections and interventional procedures.

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Table 1.1 Classification of prophylactic surgery/procedures indications[a]

Indications	Organ/pathologies
Genetic predispositions	• Breast—hereditary breast cancer • Colon—FAP, hereditary non-polyposis colorectal cancer • Stomach—hereditary diffuse gastric cancer • Pancreas—F-pancreas cancer, MEN syndromes • Thyroid—MEN1, MEN2, FMTC, Cowden syndrome • Parathyroid—MEN1, MEN2A, osteitis fibrosa cystica, FHPT • Adrenal gland—MEN2, Von Hippel Lindau syndrome, incidentaloma, etc • Syndromes—Li Fraumeni syndrome, Peutz–Jegher's syndrome, Cowden syndrome, Lynch syndrome, neurofibromatosis syndrome, FAMMM, MEN, etc • Hematologic—hereditary spherocytosis, cycle cell anemia, t, etc Associated tumors for hereditary cancers (various). • Skin—soft tissue tumors • Ovary—endometrium, etc
Precancerous lesions	• Breast—LCIS, ADH, ALH, etc • Esophagus—Barrett's esophagus • Colitis ulcerosa[a] • Biliary intraepithelial neoplasm (BillN), IPN-B, etc
Inflammations/infections (precursor lesions)	• Biliary duct strictures, cholangitis, gallstones, hepatolithiasis, etc • Cirrhosis—portal hypertension, esophageal varices • GERD—Barrett's esophagus • Colon—ulcerative colitis, etc • Pancreas—chronic pancreatitis, etc
Cystic/solid lesions (asymptomatic)	• Pancreas—IPMN, pNETs, etc • Thyroid nodules • Hemangioma, adenoma, solitary lesions (liver) • Caroli's disease, choledochal cysts, (biliary tract) • Gallbladder polyps, adenomyomas • Mass (previously had radiotherapy), etc
Morphologic disorders – Anomalia – Malrotation – Ectopy – Hematologic disorders	• Pancreaticobiliary maljunction, etc • Gallbladder anomalies, choledochal cysts, etc • Spleen—splenic artery aneurysm, wandering spleen, etc • Hematologic—hereditary spherocytosis, cycle cell anemia, ITP, etc • Colon—volvulus, diverticular disease • Gastric volvulus, etc
Miscellaneous procedures	• Transplantation[a] • Embolization [Vasculary (aneurysm, bleeding, etc), portal vein, etc] • Pringle maneuver, packing, falciform lig. flooring, etc • Bariatric surgery • Concomitant surgeries—appendectomy, cholecystectomy, oophorectomy • Vagotomy, gastroenterostomy, etc • Omentectomy, peritonectomy, lymphadenectomy, etc • Diversion procedures, etc • Percutan drainage procedures (various), etc • Compartment syndromes, etc
Others…	• Pelvic pain/exploration-appendectomy • Travel to space/pole-appendectomies, cholecystectomies (?), etc

ADH atypical ductal or *ALH* atypical lobular hyperplasia, *F* familial, *GERD* gastroesophageal reflux disease, *HPT* hyperparathyroidism, *IPMN* intraductal pancreatic mucinous neoplasm, *IPN-B* intraductal papillary neoplasia of the bile duct, *ITP* idiopathic thrombocytopenic purpura, *LCIS* lobular carcinoma in situ, *MTC* medullary thyroid cancer

[a]The table is designed to give an idea about PS. Exceptions may apply to selected patients

This section will try to explain prophylactic surgical operations and procedures with literature data and clinical practice examples.

1.1.2 Definition

Prophylaxis aims to apply approaches, surgeries, and risk-reducing procedures that will prevent the development of the disease or its complications, depending on the situations that threaten life or organs. The prophylactic procedure is a procedure that should be done naturally and at an early stage (at the most appropriate time). PS, which is the subject of our book, can also be expressed as managing risks by surgical methods. As Lord Moynihan stated as "surgery to prevent the surgery," PS is a chosen method to prevent more extensive interventions and complications [7].

Various methods are applied to the etiological factor in order to prevent cancer. The majority of cancers due to environmental factors can be prevented and reduced with protective measures. Prevention can be expressed in three different ways. There are some semantic distinctions between them. Primary prevention refers to the actual protection of the development of the disease. In contrast, secondary prevention can be expressed as an intensified early diagnosis and possible treatment options, and tertiary protection means lifetime posttreatment care. Preventive medicine and environmental health studies are essential preventive measures.

Prophylactic surgery is a concept and action developed to eradicate especially hereditary cancers while in situ. However, it is also a preferred method to eliminate complications or clinical symptoms caused by surgical procedures or developed organ pathologies, especially environmental factors that threaten organ functions without a genetic predisposition. Various procedures are made for prophylactic purposes or to reduce the risk in many asymptomatic benign pathologies.

Prophylactic interventions are advantageous in that they are more straightforward and more economical. In addition to these, it is other advantages that people increase and provide a healthier and more functional life expectancy. Laparoscopic, radiological, endoscopic, and minimally invasive surgical techniques have been increasingly used in the clinic as a result of such desire and expectation. It can be accepted that any method that provides a more comfortable or more minimal procedure than a more radical surgery has a prophylactic purpose. From this perspective, not only surgeries but also minimally invasive procedures, interventional procedures, or endoscopic procedures that will provide the same result instead of surgery should be evaluated within this framework. For example, treatment of an abscess in the abdomen not by laparotomy but by ultrasonography (USG)-guided percutaneous drainage, treatment of a severe peptic ulcer bleeding with an endoscopic approach instead of surgery, and prevention of bleeding in the spleen by embolization are also prophylactic procedures.

The procedures to be performed in diseases with genetic predisposition are briefly determining the size of the genetic transition feature after the first diagnosis, determining the risk groups, revealing screening and follow-up programs, and finally applying the prophylactic surgical procedure minimize the risk. Some clues should be questioned in order to identify patients with genetic predisposition early. These are early age cancers, cancers seen in many family members, rare tumor histopathologies, presence of the same type of cancer in many family members, presence of multiple primary tumors, bilateral cancer in bilateral organs, some racial characteristics, and unusual tumor presentations (Table 1.2). In addition to general features, clinical, radiological, and laboratory screening criteria should be determined according to its origin. Around 70

Table 1.2 The suggestive features of genetic predispositions

Mutation	Predictors
Germline	• Cancers seen at an early age (<40) • Cancer in many family members (first- or second-degree relatives) • Rare tumor histopathologies • Same type of cancer seen in many family members • Presence of multiple primary tumors • Bilateral cancer in double organs • Racial characteristics • Unusual tumor presentations • Known familial genetic predisposition
Somatic	• Radiotherapy/exposure to radiation • Exposure to chemical compounds • Infections/inflammation • Old age • Chemotherapy? • Alcohol? • Smoking?

germline mutations responsible for cancer development have been identified [8–10].

1.1.3 Diagnosis

1.1.3.1 Genetic Testing and Counseling

The first requirement of prophylactic surgical treatment in genetic diseases is the definition of germline transition characteristics. Management of patients with genetic disposition is determined according to the target organ and the mutated exon and codon (location) [11–15]. The clinical picture varies according to the location. Even by looking at the exon and codon location features, information can be obtained about whether the disease will progress aggressively and other organ pathologies. For example, in MEN2 cases, more than 80% of cases are MEN2A, 15% familial medullary thyroid cancer (FMTC), and 5% MEN2B, depending on the location of the mutation [16, 17]. Desmoid tumor is seen more than ever when the mutation in a patient's APC gene with FAP is localized between codon 1310 and 2011 [18]. Nowadays, as new exons and codons are found in hereditary diseases, more detailed information about the clinic of the diseases continues to be obtained [17]. Another critical issue for diagnosis is the variety of mutations in genes. For example, about 100 different mutations have been reported in the CDH1 gene for hereditary diffuse gastric cancer (HDGC) [19, 20].

Eighty to ninety percent of cancers occur with sporadic, 3–20% with germline-type genetic predisposition. It is estimated that about 15–25% of organ-based cancers are at familiar risk [1, 21–23]. The proportions may vary according to organ, age, breed, and race. As an example, BRCA positivity was reported as 36% in women of Jewish ancestry [24]. Stoltze et al. (2018) reported that germline-transmitted pediatric cancer syndromes are seen more than previously predicted [25]. Genetic predispositions cause FAP in 1–3% of patients with gastric cancer, 1% of patients with colon cancer, and Lynch syndrome in 1–3% [19, 26]. A study done in the USA reported that 5–9% of thyroid cancer cases were MTC and 25% of them had a hereditary predisposition [1, 17]. The presence of genetic predisposition has been detected in 5–10% of breast cancer patients and 10–15% of patients with ovarian cancer [Walsh T]. When considering disease-based, it is revealed that 20–25% of patients with MTC and 20–25% of breast–ovarian patients have a genetic predisposition [17, 27, 28].

Situations related to genetic predisposition can be examined under three main headings.

Patients with genetic predisposition constitute the largest risk group. The sensitivity, specificity, and correct performance of the test are important in determining the chosen treatment. For example, APC gene mutation can only be detected in 80–90% of the patients with FAP clinic [29]. Similarly, the presence of mutations in MLH1 and MSH2 genes can be detected in 90% of patients with Lynch syndrome (HNPCC-Hereditary nonpolyposis colorectal cancer). Apart from these two genetic mutations, it has been reported that 10% of the cases have mutations in the MSH6 and PMS2 genes [30–32]. Besides, hormones synthesized in patients with known hereditary cancer syndrome (e.g., calcitonin for MTC) may be considered as a disease-specific marker for diagnostic and follow-up purposes [17, 33].

People in the second group have a genetic predisposition in their family, but no genetic mutation. Different genetic screening and surveillance

programs are needed in these patients. According to this, some algorithms define the risk assessment tools and how the follow-up will be in people with genetic predisposition [4, 34]. The third group is the patients with familial cancer history but no data on genetic predisposition. These patients need enhanced surveillance. Algorithms that revealed the risk should be introduced. The way of surveillance varies according to the location of malignancy development. For example, 20–25% of high-grade serous ovarian carcinomas have a germline or somatic BRCA1/2 mutation. Genetic testing should be performed in all ovarian cancer cases [35].

In general, somatic mutations are usually low frequency and are only detectable by amplification of the genome. Mutations that involve less than 10% of cells in the tissue sample are generally not detectable using genome amplification strategies [4, 36, 37].

Lesions without genetic inheritance but with precancerous features are frequently encountered in the clinic. The risks of these lesions, in terms of health, should be evaluated (Fig. 1.1). For example, endoscopic and histopathologic surveillance studies demonstrate the risk of developing Barrett's esophagus due to gastroesophageal reflux and subsequent cancer development. While prophylactic esophagectomy was performed in more patients due to Barrett's esophagus and the risk of cancer development in the 1990s, today the success of endoscopic eradication reaches 95% and prophylactic esophagectomy is performed only in complicated patients. In short, the need for surgery has decreased with the development of endoscopic follow-up and diagnostic

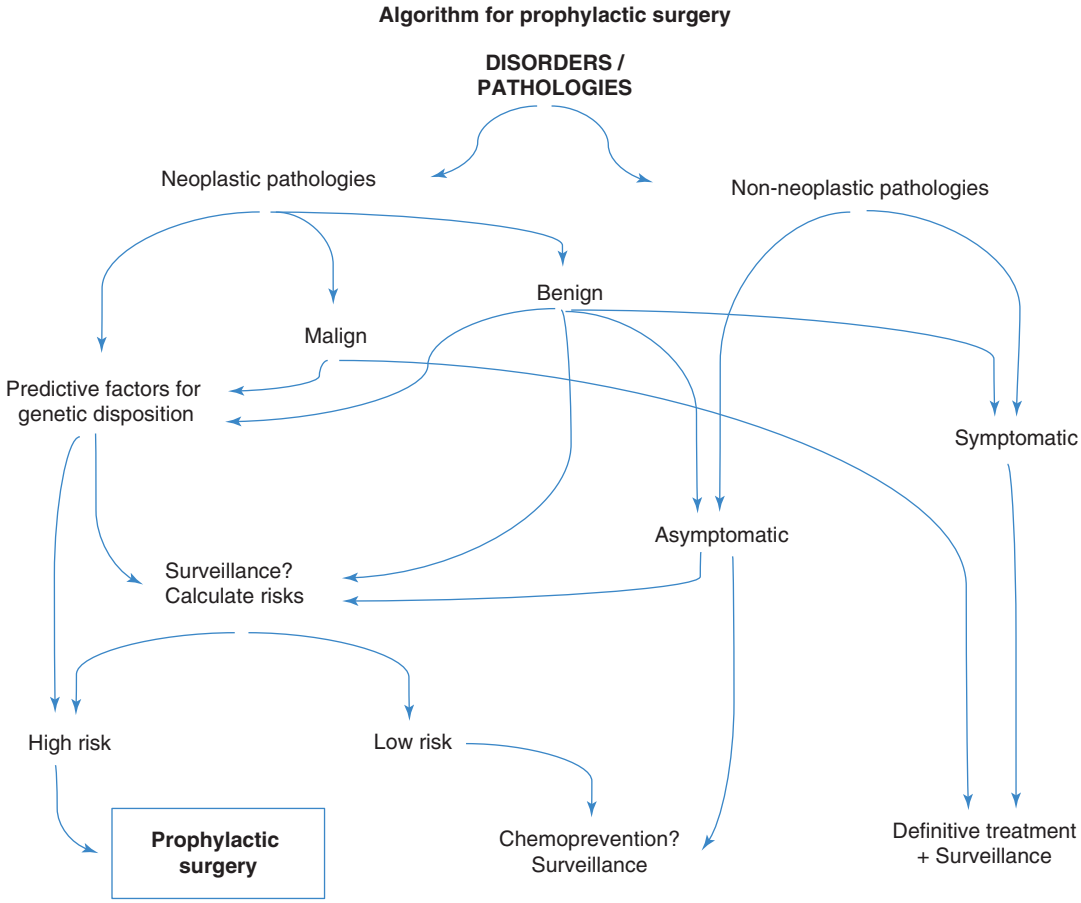

Fig. 1.1 Diagnostic and therapeutic approach algorithm for prophylactic surgery

tools [38]. The opposite situation is seen in the pancreas, and with the widespread and effective use of diagnostic tools, more precancerous lesions are detected in the pancreas, and PS is applied.

1.1.3.2 Histopathologic Evaluation

Histopathologic evaluation is important in determining the method (concurrent resections) to be applied in diagnosis, surveillance, and PS (see Chap. 27). During the diagnosis phase, sampling from an appropriate location and sufficient amount are necessary for an accurate diagnosis. Deficiencies in diagnosis and monitoring devices and biopsy are the most significant problems. For example, in the HDGC series of 23 cases by Hebbard et al. (2009), endoscopic surveillance was insufficient in detecting cancer in 91% of the cases [39]. However, in very young patients with HDGC mutation, it is recommended to take six random biopsies (minimum 30 biopsies) from the stomach parts every year until the age of surgery [40]. A definitive diagnosis can be made in 80–90% of clinically suspected patients with genetic predisposition syndrome [1, 4, 19].

1.1.3.3 Misdiagnosis

Deficiencies in the genetic analysis may cause errors and inadequacies in diagnosis and treatment. There are some studies indicating that resection may not be required in patients with incomplete mutations detected in genetic examinations performed on patients undergoing prophylactic resection [41]. Moreover, traditional mutation analysis may overlook some of the mutations that can only be detected when the two alleles are studied separately using more sophisticated techniques [17]. For example, it has been reported that in patients who underwent total gastrectomy due to HDGC, the penetrance of CDH1 mutation was incomplete and unnecessary resection was performed in up to 20–30% of these patients. The unnecessary resections may be due to diagnostic errors due to inadequate biopsies and the unclear surgery date for HDGC [4, 37, 42]. There are "missense mutations" in 26% of MLH1 mutations and 16% of MSH2 mutations defined in Lynch syndrome. Clinically, APC mutation cannot be detected in 10–30% of patients with FAP [41]. Misdiagnosis may be due to deep intronic mutations, genomic rearrangements, missense mutations, and mutations in other genes that have not yet been identified or further characterized. Such situations make it difficult to evaluate the data [43, 44].

1.1.4 Surveillance

Patient follow-up should be considered in various aspects. It will be necessary to prepare and implement separate follow-up programs in basic issues such as the follow-up of patients who will be operated, patients with low genetic risk, patients without surgery, and their relatives. The surgical age of patients with genetic predisposition is generally recommended as 5–10 years earlier than the youngest patient in the family. It should be determined at what age patients will be operated and how to follow until this age [42]. However, the recommended surgery ages may vary depending on the sick organ and its genetic (exon codon) characteristics [19, 45–48]. Besides, it is known that patients with hereditary cancer syndrome have a high risk for second primary tumor [28, 45].

There are surveillance programs that specify how monitoring will be done. For example, it is recommended to perform surgery for MTC in the first months after birth in patients with MEN2B, before 5–6 years of age in children with MEN2A mutation, and between 5 and 10 years of age in familial-type MTC cases, or according to calcitonin level [15, 49, 50]. In families diagnosed with DHGC, prophylactic gastrectomy is recommended at the age of 5 years younger than the youngest patient for certain hereditary transmission [19, 51]. In families with FAP, endoscopic control is recommended from the age of 10 to 12, and from the age of 25, an annual gastroduodenoscopy, thyroid USG from the age of 10, and abdominal USG and AFP level follow-up for hepatoblastoma from the age of 5 are recommended [52, 53].

In the lifetime follow-up of patients with Lynch syndrome, it was reported that 54% of the

cases developed endometrial cancer and 10–12% of them developed ovarian cancer [45]. Patients with Lynch syndrome to have a colonoscopy every 1–3 years before the age of 20–25 for the follow-up of colonic pathologies, transvaginal USG, and pathologic examination of endometrial aspiration once a year before the age of 30 for extracolonic organ scanning, especially for the endometrium and ovary, and the examination of CA-125 in blood recommended [8, 9, 54]. Jarvinen et al. (2000) reported that mortality decreased 65% in families with Lynch syndrome in which they applied a 15-year surveillance program [55]. It has been reported that retained rectum cancer developed in 12% of the patients who preferred subtotal colectomy for Lynch syndrome during the 10–12-year follow-up [56].

While high-risk patients with a genetic predisposition are operated, patients considered low-risk should also be followed up. For example, a low-risk thyroid patient should be followed up with USG and biopsy when necessary, and risk analysis should be performed. Similarly, periodic colonoscopy for colorectal carcinoma, endoscopy for the stomach, MRI for breast cancer may be required. There are surveillance programs established for each organ, and developed algorithms should be followed [2, 9, 34].

The prophylactic surgical procedure is aimed to be curable. However, a complete cure may not be achieved in patients whose target organ is removed. Surveillance programs should also be made for patients undergoing surgery. For example, the risk can be reduced up to 95% in people who undergo prophylactic mastectomy. In cases where the resection is thought to be incomplete, it may be necessary to follow the risky areas (chest wall for breast cancer) [2, 34]. Similarly, in patients planned to undergo an ileorectal anastomosis due to FAP, periodic control of the mucosa left in the anorectal part is required [57].

There is a risk of malignancy development in other organs in some patients who undergo surgery for hereditary cancer. The risky organs should be followed up. For example, it is reported that the lifetime risk of developing hyperparathyroidism as 95%, pancreas-NET development as 40–70%, and pituitary-NET development as 30–40% in the follow-up people with MEN-1 syndrome (Wermer syndrome), which is very rare [58]. Adrenal cortical tumors, carcinoid tumors, lipomas, angiofibromas, gastrinomas, and meningiomas may also develop in these patients [58–60]. While MTC develops in 100% of the patients with MEN2A syndrome, pheochromocytoma may develop in 50% of all MEN2 cases, and hyperparathyroidism may develop in 25% [15, 50]. According to The American Thyroid Association (ATA) criteria, patients with risk for pheochromocytoma and high-risk alleles should be followed at age 11 and patients with moderate risk at the age of 16. Plasma-free metanephrine and nor-metanephrine and urine nor-metanephrine levels should be monitored during follow-up. MRI and CT scanning are also recommended for people with average blood values [60].

While adenomatous polyps develop in 95% of APC gene mutation carriers for FAP before 35, cancer develops in 90% of the cases before the age of 50. Total colectomy to be performed in patients with FAP is very important for the cure. However, it should not be forgotten that the upper gastrointestinal system malignancies and progression of desmoid tumors encountered during the patients' course are the most important causes of mortality [1, 61]. Patients will need to be followed up by endoscopic and radiological imaging methods.

The lifetime risk of developing breast cancer in BRCA1/2 positive individuals is 50–85%, and the risk of developing ovarian cancer is calculated as 10–46% [62–64]. Similarly, it has been reported that 20–60% of patients with Lynch syndrome who are followed up for life develop endometrial cancer, and 5–12% of them develop ovarian cancer [45].

People with E-cadherin/CDH1 gene mutations have a lifetime risk of HDGC development of 70–80%. Also, 67% of male patients and 83% of female patients risk developing breast cancer [62, 63]. Surveillance programs are recommended because of the increased incidence of lobular breast carcinoma (lifetime risk 40–60% for females), colorectal, and prostate cancer in patients undergoing total gastric resection due to

HDGC [65]. Similar follow-ups are performed for nonneoplastic pathologies. It is essential to use diagnostic methods such as MRI and EUS to follow-up for cystic lesions of the pancreas. In contrast, endoscopic follow-up is vital for patients with Barrett's esophagus. The algorithms developed and recommended by international organizations (e.g., ATA, AGA-American Gastrointestinal Association) within the framework of evidence-based medicine in this regard are instructive.

In addition to the diagnosis, follow-up, and PS of hereditary cancers, it should also be evaluated in terms of environmental, familial, economic, social, and psychological dimensions.

1.1.5 Chemoprevention

Chemoprevention is an option that can be applied to protect other target organs in the nonoperative, low-risk group, or postoperative period. There are different medications and approaches for each disease. For example, selective COX-2 inhibitors and nonsteroidal anti-inflammatory (Sulindac) drugs are the most commonly used drugs in patients with FAP [66–68]. In the series by Tonelli et al. (2000), it was reported that the number of polyps decreased by 28% with the use of COX-2 inhibitors for 6 months. However, the diameter of the polyps increased, and the number increased within 4 years after discontinuation of the drug [69].

Prophylactic surgery can be delayed with chemoprevention. Special conditions of the patients may require this. For example, tamoxifen is the most used drug in breast patients. Whether the woman has a child, her age, and her fertility age are important for use. Due to BRCA2 positivity, women who do not have children and who are of childbearing age may request the surgery to be delayed. In such patients, periodic diagnostic screening programs are also applied in addition to tamoxifen treatment for chemoprevention [42, 70, 71].

Elective surgical interventions were postponed worldwide due to the global Covid-19 pandemic in recent months, except emergency and tumor. PS for cancer and noncancer cases had been deferred for 3 months in the USA and UK [72–74]. In patients with genetic predisposition, chemoprevention can be applied as an option in similar cases where surgeries will be delayed. Longer follow-up and surgery can be performed in patients who can be followed closely with diagnostic tools. The issue of chemoprevention in non-tumor cases is more comprehensive and controversial. Prophylactic procedures for many nonneoplastic pathologies are described in detail in the chapters.

1.1.6 Prophylactic Resections

In order for resections performed to get rid of hereditary cancer to be prophylactic, the entire target mass should be removed. For this purpose, defined surgical protocols are needed for each organ. The surgeon and pathologist should cooperate very closely in this regard. For example, total thyroidectomy with posterior capsule and central lymph node dissection is recommended for MEN2 patients as prophylactic. Because of the risk of hyperparathyroidism, parathyroid glands are also recommended to be removed in the same surgery and transplanted into the forearm muscle (autotransplantation) [11, 15, 75].

It has been reported that total gastrectomy and D1 lymph node dissection are sufficient for HDGC carrier, and D2 lymph node dissection is not required [76]. The surgery can be done more easily by the laparoscopic or robotic method. However, in order to understand that the procedure is complete, it is recommended to confirm by the frozen section that the specimen has a ring consisting of the duodenal mucosa at the lower end and the esophageal mucosa at the upper end. Implementation of this protocol is required to prevent future relapse [51].

Prophylactic surgeries' protection rate varies between 80 and 95% despite all the resections performed [1, 19, 77, 78]. Inadequate processing, diagnostic deficiencies (unknowns), and accompanying other organ pathologies are the most important causes of morbidity and mortality.

Many organ resections are performed for nonneoplastic reasons. Among these, prophylactic esophagectomies, which were performed extensively in the 1990s to prevent adenocarcinoma due to Barrett's esophagus, have decreased today due to the success of endoscopic eradication. Prophylactic/incidental appendectomy is the most common PS performed for nonneoplastic reasons (see Chap. 18). Although pancreatic IPMNs are closely monitored due to the high risk of malignancy, prophylactic pancreatic resections have to be performed in cases where the risk increases (see Chap. 10).

1.1.7 Concurrent Surgeries

It should be questioned whether other target organ resections will be added to the procedure in patients with genetic predisposition undergoing PS. For example, prophylactic mastectomy and oophorectomy should be planned together in BRCA2-positive individuals. Adding hysterectomy to the procedure during prophylactic colectomy in patients with Lynch syndrome is one of the most common concurrent surgeries. Especially in patients with MSH6 mutation, the risk of developing endometrial cancer is higher, and concurrent prophylactic hysterectomy is recommended [30, 45]. In ovarian tumors with a hereditary transmission characteristic up to 20%, oophorectomy may not be sufficient, and tumors can be seen in the tubules. In such cases, additional resections will be added to the process, and close follow-up of patients will be required for cases that cannot be added to the process. The situation is similar for uterine cancers [27]. There are similar situations for MTC, and parathyroidectomy is added to the procedure. It is described in more detail in the sections on organs.

Incidental (concurrent) organ resections or procedures are added to the process in some interventions performed for cancers or noncancer reasons. For example, some authors recommend prophylactic cholecystectomy because of the increased risk of cholelithiasis and choledocholithiasis in cases where duodenum is bypass or Roux-en-Y [79, 80]. Incidental appendectomy is one of the most common procedures performed in patients undergoing exploration due to pelvic pain [81].

1.1.8 Postoperative Evaluation

Histopathological examination is essential in understanding whether the prophylactic procedures performed are sufficient or not. For example, endoscopically eradication can be achieved in 87–96% of Barrett's esophagus cases, which is the main cause of esophageal adenocarcinoma [38]. In cases with endoscopic mucosal resection, it should be evaluated whether the specimens removed are sufficient or not, especially in terms of the risk of remaining buried mucosa [82]. The risk of inadequate resection also applies to patients undergoing total prophylactic colectomy or total gastric resection for genetic predisposition. It is well known that the risk of tumor development continues in cases with insufficient resection.

Pathologists should investigate whether there is a tumor focus in each case. Occult cancer foci can be detected in some cases with careful examination of the specimens after PS. In a study of 90 cases conducted in the USA, 15% of the patients who underwent prophylactic mastectomy and oophorectomy due to BRCA2 positivity had ductal carcinoma in situ, 8% invasive ductal carcinoma, 3% fallopian tube adenocarcinoma, and 3% ovarian adenocarcinoma [83]. In another example, Groot et al. (2006) operated 20 MEN2 patients (mean age 10) with RET mutations and found C-cell hyperplasia in 19 patients, MTC (70%) in 14 cases, and lymph node involvement in 3 patients on histopathological examination [84]. In another FMTC series of 16 cases, it was reported that the tumor was multifocal in 13 cases, bilateral in 11 cases, and desmoplastic stroma in all cases. It has also been reported that lymph node metastasis is more common in cases with desmoplastic stroma [85]. These results indicate that the patients with genetic predisposition should be operated at a much younger age.

1.1.9 Recommendations for Prophylactic Surgery

Since prophylactic surgical procedures will not involve some radical tumor surgery procedures, they will be more easily applicable procedures. Most prophylactic procedures can be performed using laparoscopic, endoscopic, and radiological interventional procedures depending on technological developments. PS may become a separate discipline in the future.

The following rules should be followed in patients undergoing PS due to genetic predisposition in tumors [1, 21, 42];

1. Must have a high genetic predisposition (independent from environmental factors).
2. The diagnostic test must be reliable.
3. Cure with surgery should be possible.
4. Surgery should be performed with minimal morbidity and mortality.
5. In the absence of organ/tissue, insufficiency (disability) should not be seen, or its maintenance should be provided.

Rules to be followed in patients who are planned to undergo PS for non-tumor reasons:

1. A definite diagnosis should be made.
2. Especially life-threatening complications and their consequences should be anticipated/known.
3. It should be done with minimal morbidity and without mortality.
4. In the absence of organ/tissue, insufficiency (disability) should not be seen, or its maintenance should be provided.
5. Surgery should be able to cure or prevent complications.

Rules to be followed by the surgical team and center:

1. The decision for surgery should be taken with the knowledge and approval of the patient and his family.
2. A decision should be made with a commission consisting of experts from different disciplines (surgeon, radiologist, pathologist, psychiatrist, and related branches).
3. The operation center must be experienced (especially for genetic predisposition).
4. Must have the infrastructure to manage complications.

1.1.10 Cost-Effectivity

There are many studies on the cost-effectiveness of screening and surgeries to be performed due to genetic predisposition. For example, Ramsey et al. (2001), in the genetic screening study conducted in families with Lynch syndrome, performed the cost analysis of patients who underwent screening study with a standard approach. Savings of $ 7556 per patient were reported for each year earned as a result of screening [86]. The general opinion is that PS is cost-effective (see Chap. 4).

1.1.11 Quality of Life (QoL)

Prophylactic surgery can protect patients from the impending danger in 80–95% of cases. It affects the quality of life (QoL) psychologically and, in general, positively. However, it should be kept in mind that the procedure is irreversible and has many side effects and complications in the long and short term. Razdan et al. (2016) reported that 61–100% of the patients in various series undergoing prophylactic mastectomy and oophorectomy considered PS satisfactory [87]. The QoL was found to be lower in those who had surgery due to FAP due to the size of the surgery and accompanying bowel habit problems [88]. Postoperative morbidity and 0–4% mortality are seen in 60% of the patients who undergo total gastrectomy for HDGC. Mental, emotional, and physical problems encountered in the first months of the operation return to normal within 6 months to 1 year in most patients [89, 90].

Education and psychological support of patients and families can provide better diagnosis and treatment [91, 92]. Eliminating the

complications that may develop due to the disease with PS especially the anxiety that occurs due to the risk of cancer relieves and the QoL increases.

1.2 In Conclusion

Prophylactic surgery aims to eliminate the target organ before the life-threatening disease develops, increase the expected survival, and prevent the decrease in the quality of life. The term "prophylactic surgery,"which indicates preventing the probable event before it occurs, has become more popular and gained importance by the current advances in medical literature, surgical techniques, and biomedical equipment.

Experienced centers should follow up the patients with genetic predispositions, and advanced diagnostic tools and specialist doctors.

Early diagnosis will result in a higher chance of cure, more comprehensive surgery, fewer complications, less mortality, lower cost, longer survival, and improved quality of life.

Increasing the detectability of mutant genes, mainly in genetically inherited cancers, will result in high surveillance, prevention, and surgical interventions for prophylactic purposes will become more important.

Surgical resections will begin to be performed in a different size, with a minimally invasive surgery technique. As the pathophysiology of the diseases is well understood, PS will find more application areas in our future lives and surgical clinics with its wide variety of dimensions.

Prophylactic surgery will take its place in the future as a discipline with a corporate identity that adopts a multidisciplinary approach.

The cost-effective dimension of PS will appear as new problems that should be evaluated in the future by insurance companies and health service providers.

Legal, ethical, social, and psychological dimensions of prophylactic initiatives will need to be examined with wide and multicentric center participation.

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2 Minimally Invasive Procedures and Prophylactic Surgery

Viktor Justin and Selman Uranues

2.1 Introduction

The aim of preventive surgery is to preclude the development of diseases and/or their long-term effects, and consequently to reduce morbidity and mortality. In this context, the old dogmas "*primum nihil nocere*" *(first, do no harm)* and "*the cure must not be worse than the disease*" are of highest importance. A procedure that aims to prevent a disease can be considered as being highly elective, and morbidity as well as complication rates must be as low as possible and acceptable. These procedures are often performed on active healthy persons in working age and thus should aim to be effective in prophylaxis with minimal strain on patient health and quality of life. That also includes fast recovery resulting in early reintegration into daily life and minimal socio-economic cost.

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2.2 Historical Remarks

While surgical interventions date back millennia, modern surgery started with the onset of anaesthesia and the first ether narcosis in 1846 [1]. Almost at the same time, Semmelweis published his observations on puerperal fever leading to a new understanding of post-operative infections [2]. While Semmelweis was mainly ignored, further research by Pasteur, Koch and Lister led to the general use of antisepsis and consequently to the further improvement of surgical outcomes [3, 4]. The discovery of antimicrobial therapy was another milestone for better surgical outcomes enabling major surgeries for all kinds of indications [5]. Following decades of continuous development, the advent of minimally invasive procedures marked the next revolution in surgery. While the first laparoscopy for diagnostic indications was described in the early 1900s [6], its therapeutic use was only slowly implemented after several years of (at times fierce) discussions in the 1980s, with laparoscopic appendectomy and cholecystectomy being the first indications [7, 8]. Since then minimally invasive surgery (MIS) has gained wide use with the constant development of new technologies including reduced port surgery, which aims at a reduction in the number and size of the ports. The use of robotic techniques has led to an additional expansion of the armamentarium of the minimally invasive surgeons.

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2.3 Learning Curve in Minimally Invasive Surgery

Mastering a surgical skill requires time and intensive training, which can be described by a *learning curve*, a concept initially postulated in aviation. In surgery, talent is supplementary and does not replace training and experience [9]. While there is no strict definition, learning curves are usually drawn by comparing patient outcomes and/or measures of efficiency (complications, duration of operations, rate of conversion, adequate oncological resection, etc.) to surgeon experience *or* case load [10]. While often wrongly used, a steep learning curve implies fast mastering of a procedure, while complex operations need higher caseloads resulting in a longer and gradually inclining curve. An acceptable standard is reached when a surgeon is able to perform the procedure independently and competently. From here on, further experience only slightly improves outcomes leading to a plateau that has to be maintained by a certain annual case load. Interestingly, a so-called secondary learning curve has been observed, describing a temporary decline in performance after a certain level has been reached. This may be explained by more complex cases, or overestimation of own competence and skill. Finally, a certain deterioration in performance may be observed with advancing age.

In a comparative study of individuals without surgical expertise, laparoscopic surgery was perceived to be more difficult to learn than open surgery [11]. To reach a stable skill level in MIS, about 30–80 cases as necessary for colorectal surgery, 80 cases for thoracoscopic anatomic lung segmentectomy and 150 cases in esophagectomy [10, 12, 13]. However, these numbers may vary substantially depending on pre-existing skills, annual case load and previous expertise. This can be illustrated by results for the implementation of minimally invasive pancreatic surgery, where centres with high expertise in open surgery reported good results after a very short learning curve of ten cases, while centres with a low annual number of resections per surgeon had worse outcomes [14–16]. Apart from possible short- and long-term morbidity, surgical complications may also have a significant impact on psychosocial well-being even long after the operation [17].

Consequently, preventive minimally invasive surgery should not serve as a learning procedure and should only be undertaken by skilled surgeons who have mastered the learning curve for the respective indication and are performing these procedures on a regular basis.

2.4 Surgical Stress Response

By its very nature, surgery is invasive and as such triggers a *surgical stress response* that impacts a variety of organ systems (Fig. 2.1). Cortisol levels increase due to raised adrenal stimulation via adrenocorticotropic hormones (ACTH), resulting in immunomodulation and increased insulin resistance, and thus elevated glucose levels [18, 19]. The resulting post-operative hyperglycaemia has been shown to be a significant risk factor for surgical site infections and consequent morbidity [20]. Immunological changes leading to immunosuppression, such as a reduction of natural killer cell toxicity, and t-cell responses have been observed [21, 22]. Post-operative metabolism tends to increase catabolic characteristics with proteolysis especially affecting muscle tissue [23]. Apart from surgical trauma, other factors such as patient comorbidities as well as the type of anaesthesia, including perioperative analgesia and fluid support, may influence stress response [18]. Concepts such as *fast-track surgery* and *enhanced recovery after surgery* (ERAS) have been proposed to reduce morbidity [24–26]. While these should be incorporated into clinical practice generally and in preventive indications specifically, they will not be further discussed here.

MIS has been shown to reduce operative trauma significantly. Post-operative cortisol levels are lower after minimally invasive surgery indicating a lower neuro-hormonal stress response [27–29]. A randomized trial in patients undergoing lobectomy for peripheral bronchogenic carcinoma observed a significantly lower

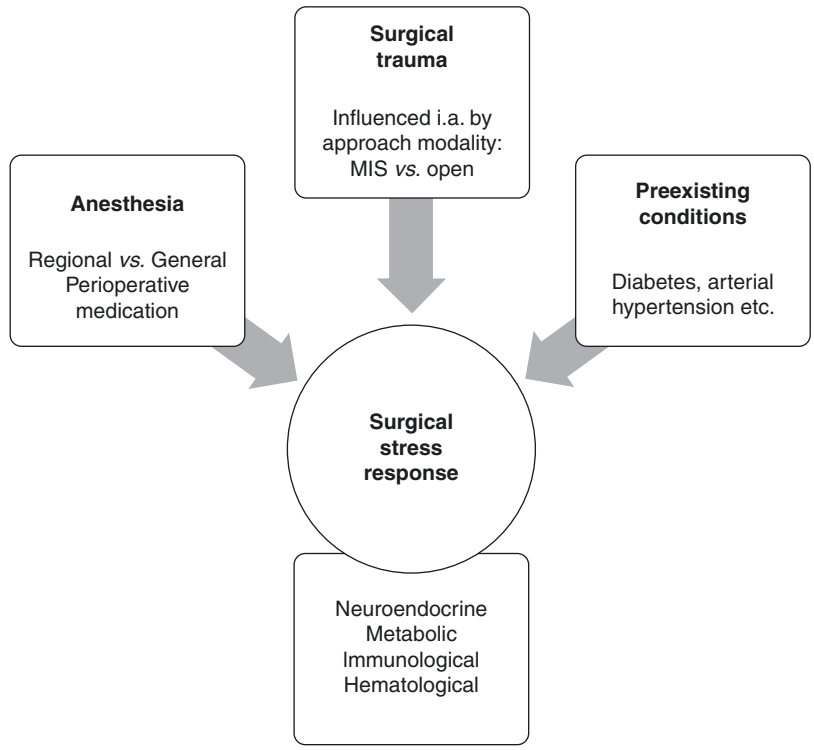

Fig. 2.1 Surgical stress response. (Adapted from [18] with permission from Elsevier)

grade of leucodepletion and a reduced degree of immunosuppression (as measured by T-helper cell depression and NK cell numbers) after video-assisted thoracic surgery (VATS) compared to open surgery [21]. Similar results in favour of minimal invasive surgery have been reported in several indications including oesophageal resections [30], cholecystectomy [28], colorectal [31–33] and hepatic surgery [34].

2.5 Perioperative and Short-Term Outcomes

MIS usually yields longer operative times [35]. However this difference is often no longer than several minutes and seems to decrease with experience [14]. Estimated blood loss has been shown to be significantly lower both in laparoscopy and thoracoscopy [35–40] Conversion rates to open surgery vary according to indications and patient selection criteria but generally lie around 10% and below in dedicated centres for visceral, thoracic, gynaecological and urologic MIS [41–43]. In laparoscopic pancreatic surgery however conversion rates up to 34% are still reported [14]. The risk of severe post-operative complications (Clavien-Dindo IIIb or higher) does not differ significantly between open and minimally invasive surgery [44].

Post-operative pain has been reported to be lower after MIS [28, 45] as well as the rate of surgical site infections (SSI) [36, 45, 46]. A meta-analysis found that SSI can be reduced by 70–80% in obese patients when laparoscopy is employed [47]. The duration of hospital stays is shorter after MIS and leads to a quicker return to daily life [14, 35, 45, 48, 49].

2.6 Long-Term Outcomes

Long-term procedure–related complications depend on the respective primary operation. In abdominal surgery, formations of adhesions and subsequent bowel obstruction, as well as development of incisional hernia, are of major concern [50]. A review of more than 440,000 abdominal

operations showed a higher incidence of small bowel obstruction (SBO) after open cholecystectomy (7.1% vs. 0.2%), abdominal hysterectomy (15.6% vs. 0.0%) and adnexal operations (23.9% vs.0.0%) when compared to their laparoscopic "counterpart" [51]. Incisional hernia occurs in about 9.9% of cases after elective laparotomy (11% midline vs. 4.7% transverse incision; $p = 0.006$) and statistically is thus significantly more often than in laparoscopy (0.7%; $p = 0.001$) [52]. Apart from individual risk factors for incisional hernia such as obesity and smoking, a history of SSI additionally increases the incidence of hernias.

While complications remain the most decisive factor for impaired post-operative quality of life, certain studies also indicate a higher post-operative QOL in minimally invasively operated individuals [53–56].

In order to round up this chapter with a practical example, applicable data from a meta-analysis from Tan et al. [57] will be utilized. A 38-year-old man, whose father died of colon cancer at age 40, has been tested positive for hereditary nonpolyposis colorectal cancer (HNPCC). He has been informed extensively and—nearing the age of his father's diagnosis—desires prophylactic colectomy. He is physically active and healthy, with a history of hypertension on his medical record. Your institution is a dedicated high-volume laparoscopic colorectal centre. You schedule him for laparoscopic proctocolectomy with ileo-rectal J-pouch anastomosis with protective ileostomy closed after 6 weeks.

The operation went as planned (Fig. 2.2) and took 3.2 h, about 30 min longer than the open approach. Estimated intraoperative blood loss was 336 mL (as opposed to 412 mL in open surgery) and no blood products were needed. Bowel function recovered after 2 days, an average 2 days earlier than after open surgery. He is one of 85% who do not develop an anastomotic leak and leaves the hospital after 6 days (a mean of 2.6 days earlier than he would have with open surgery). The small skin incision at the specimen extraction site heals without complications (Fig. 2.3). When you see him again after 6 months, he reports 3–5 bowel movements per day without strong urgency. As you adhere to compliance policy at your institution, all he can give you is a

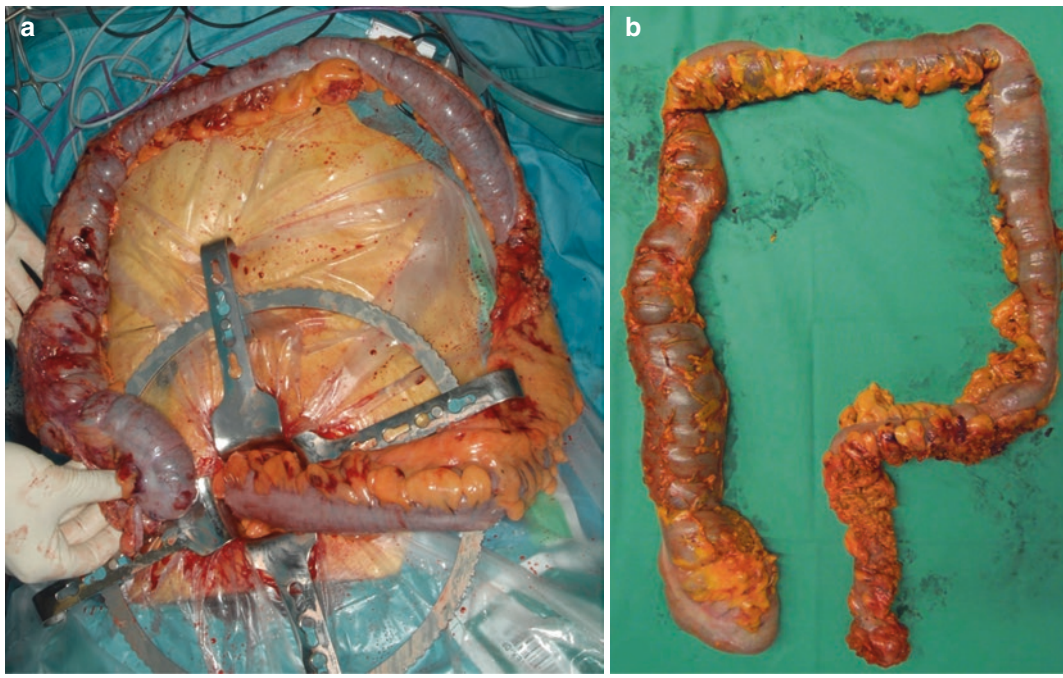

Fig. 2.2 Specimen after laparoscopic proctocolectomy: intraoperative (**a**) and back-table (**b**) view

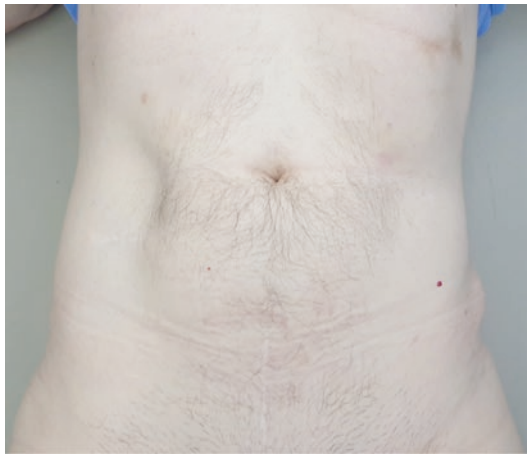

Fig. 2.3 Two-year follow-up after laparoscopic procedure shown in Fig. 2.2

big "thank you" and a firm handshake. And while this case may be idealized: Is not that what you would want for all your patients?

2.7 Conclusions

Given adequate resources and a high level of skill, minimally invasive surgery is the desirable approach in prophylactic indications. Operative trauma, post-operative pain and the risk of long-term complications (SBO, hernia) are reduced, while fewer surgical site infections and shorter length of hospital stay can be observed.

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3 Prophylactic Approaches in Abdominal Wall Surgery: Preventing and Repairing the Burst Abdomen

Rifat Latifi, James Choi, Shekhar Gogna, and Selman Uranues

3.1 Introduction

In the United States alone, roughly 350,000 ventral hernias are repaired annually [1, 2], at a cost of approximately $3.2 billion dollars, representing a major burden on healthcare resources. Additionally, emergency repairs and postsurgical complications associated with the procedure are significant [3]. Although there are individuals who may live with ventral hernias for some time before considering repair, the quality of life, impaired body image, continuous enlargement, and further loss of abdominal wall domain, as well as the risk of acute complications and the need for emergency surgery, are the main reasons for prophylactic surgery in complex abdominal wall defects. If left untreated, complex abdominal hernias can lead to hospitalizations and life-threatening bowel (large and small) obstruction, although the exact number of these events is unclear.

Abdominal wall (incisional) hernias are common. A large retrospective study of 2983 patients followed over a 10-year period found that in 31.5% of cases incisional hernias occurred 6 months after abdominal surgery. This number increases to as high as 88.9% after 5 years [4]. The further a patient is from their original date of surgery, the higher the risk for hernia recurrence.

Should an incisional hernia occur, the risk of incarceration and strangulation is dependent on the size of the defect. Significant factors that contribute to incisional hernia are age >45 years, BMI >25, and male gender. Patient comorbidities, technical factors of surgery (large vs. small suture bites), and disease factors (wound infection, defect size) also contribute to the etiology of incisional hernia occurrence. Other patient factors, such as smoking and diabetes mellitus, have also been shown to decrease wound healing and increase hernia recurrence. Yet, in our opinion, the most common causes of recurrent hernia are the experience of the surgeon and the technique used for repair [5]. A detailed description of techniques used in repairing the abdominal wall defects is beyond the scope of this chapter, as there are numerous textbooks and papers describing various approaches: from open to laparoscopic, to robotically assisted repair.

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3.2 The Burst Abdomen

An acute postoperative open abdominal wall (POAW), also known as a burst abdomen, is a postoperative complication associated with mortality rates as high as 45% [6, 7]. Overall, the incidence of this abdominal complication may vary from 0.5 to 3% of all laparotomies, but the postoperative incisional hernia rate is at an alarming 40–60% [8–10]. Emergency operations, wound infections, elderly age, or persistent increases in intra-abdominal pressure postoperatively (such as coughing or retching) are only some of many predisposing factors that can increase the risk of the development of POAW [11]. The most common cause of acute burst abdomen is poor surgical technique or unrecognized intra-abdominal hypertension syndrome. Other major causes are intra-abdominal infections or postoperative catastrophes. Although a burst abdomen may occur within 24 h after surgery, POAWs are generally seen an average of 7 days postoperation [12].

Treatment for POAWs remains patient-specific but several options have been studied. For patients with incomplete dehiscence without the presence of adherent bowels, primary fascial closure using absorbable monofilament has been suggested [13]. We disagree with this approach, and perform definitive closure of the abdomen to avoid further catastrophes such as open abdomen, entero-cutaneous or entero-atmospheric fistulas, and other major complications of an open abdomen [14–17]. In the absence of intra-abdominal infection (in cases when the burst abdomen is a result of poor surgical technique), synthetic mesh may be used to reinforce these abdominal wall closures. The use of biological mesh in contaminated or clean-contaminated fields in this patient population has been limited. In recent years, our group has been using biologic mesh in all contaminated or clean-contaminated cases [16, 18, 19]. In dirty or contaminated wound, we do not close primary the skin edges. Instead we use delayed primary closure technique and negative pressure therapy systems (Prevena™) [6].

3.3 Prophylactic Mesh Placement

3.3.1 Elective Surgery

Current European guidelines state that abdominal wall closure should be achieved using a slowly absorbable suture in a running technique [20]. However, the type of optimal suture material has not been established. The STITCH trial was a multicenter randomized clinical trial looking at small versus large bites in surgical and gynecological departments to close elective laparostomies. In the end, a small bite suture technique (5 mm bite every 5 mm) was regarded as more effective for the prevention of incisional hernias for midline abdominal wall incisions. In this study, the incisional hernia rate after 1 year was found to be 13% in the small bite group versus 21% in the large bite group [21], which in our opinion is very high for elective surgery. Another study performed in animal models showed that risk of dehiscence is lower when stitches are placed 3–6 mm from the wound edge compared to 10 mm [22]. This technique has also been beneficial in multiple other studies such as the MATCH (Meta-analysis on Materials and Techniques for Laparotomy Closure) review [23]. Unfortunately, even after a running, slowly absorbable suture closure of the abdominal wall, there is a 10 and 30% risk of incisional hernia on long-term follow-up [24, 25]. In our practice, we perform "en masse" continuous closure using slowly absorbable sutures. In cases of a burst abdomen, or patients with a high risk of dehiscence, we will perform definitive abdominal wall closure using posterior component separation technique, or sublay placement of biologic mesh [16].

However, despite these various technical advancements in primary abdominal wall closure, the incidence rate of postoperative incisional hernias can be as high as 13% [26]. In recent years, the technique of prophylactic mesh placement in elective abdominal wall procedures has become more common [27, 28]. Prophylactic abdominal wall surgery is defined as the placement of mesh placement during the time of elective abdominal

surgery. A randomized control trial conducted by Payne et al. reviewed the use of synthetic mesh to reinforce midline laparotomy incisions in 169 patients undergoing elective abdominal surgeries [29]. Although there was no difference in rates of surgical site infection (SSI), the incidence of hernia recurrence was significantly less after 1–3 years. Not surprisingly, the time to complete wound healing in patients with SSIs was significantly longer. Currently, the European Hernia Society suggests that prophylactic mesh reinforcement can be performed for elective midline laparotomies even in high-risk patients (i.e., abdominal aortic aneurysm or patient with BMI >30), however the evidence to support this approach is weak [20]. We believe that this acceptable adjunct procedure will prevent major hernias in this group of patients.

The PRIMA (Prevention of Incisional Hernia With Prophylactic Onlay and Sublay Mesh Reinforcement Versus Primary Suture Only in Midline Laparotomies) trial was a 2-year, multicenter, randomized control study covering 11 hospitals from Austria, Germany, and the Netherlands [30]. The primary goal was to evaluate the long-term incidence recurrence rates after elective midline laparotomy. Patients had an abdominal aortic aneurysm or body mass index $\geq$27 kg/m^2. Onlay and sublay mesh placement was compared with primary closure technique. Of the patients who were found to have incisional hernias, those who underwent primary closure exhibited the largest rates at 30%, followed by sublay (18%) and onlay (13%). Wound infection rates were similar among the groups; however, seromas were more frequently observed in onlay mesh placement.

A systematic review conducted in 2017 found that prophylactic synthetic mesh placement in elective abdominal wall surgery decreased the risk of postoperative incisional hernia by 85% when compared to primary closure alone [31]. Patients of prophylactic mesh placement were also at an increased risk of chronic surgical site pain compared to primary closure. Similar to the PRIMA trial, onlay synthetic mesh position was associated with an increased risk of seroma formation. For these two reasons, we prefer the use of biologic mesh, although long-term data on this are lacking [32].

3.3.2 Emergency Surgery and Prophylactic Mesh Placement

It has already been shown that the use of prosthetic mesh at the time of laparotomy can reduce the incidence of postoperative incisional hernias [1, 28–31, 33]. However, the use of mesh in emergency surgery is a matter of great debate. At the heart of the argument is whether the placement of nonabsorbable materials should be used in potentially infected fields, i.e., after intestinal resection, bile duct operations, or parastomal hernias repairs. Finding the correct indication in these situations remains a difficult task. In situations where frank contamination is present, the general consensus is to avoid the use of prosthetic material all-together [34]. However, there has been a lack of consistent evidence in regard to mesh placement during simultaneous operations on the gastrointestinal tract, especially in the emergent setting. The Ventral Hernia Working Group (VHWG) guidelines recommend against the use of synthetic mesh if the risks of wound complications are high, a sentiment that is echoed by the European Hernia Society [20, 35]. However, a recent prospective multicenter study conducted in the Netherlands examined biological mesh closure versus temporary abdominal closure in emergent nontraumatic patients. Although the sample size was 20 patients in each group, they found that closure with biological mesh resulted in a significant reduction of ICU length of stay and reoperations [36]. At the senior author's (RL) busy practice, there has been a paradigm shift regarding early abdominal wall closure using biological mesh after trauma, intra-abdominal catastrophe, and damage control surgery [37]. Figure 3.1 illustrates a chronically infected abdominal wall wound extending to the abdominal fascia, which was excised and underwent a posterior component separation with bio-

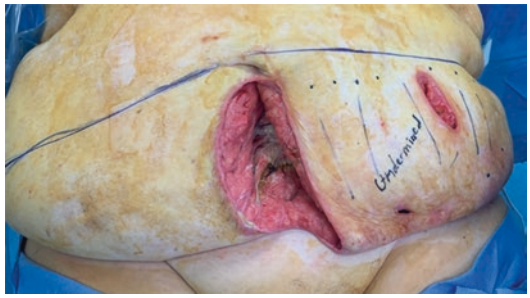

Fig. 3.1 Chronically infected abdominal wall wound extending to the abdominal fascia with undermining to the left lower quadrant

logical mesh placement during the same time as her wound debridement (Fig. 3.2).

3.3.3 Use of Biologic Mesh

As the techniques of abdominal wall hernia repair continue to advance, the focus on finding the ideal mesh material also continues alongside these developments. While synthetic mesh reinforcement has been shown to be more cost-effective when compared to the burden of readmissions

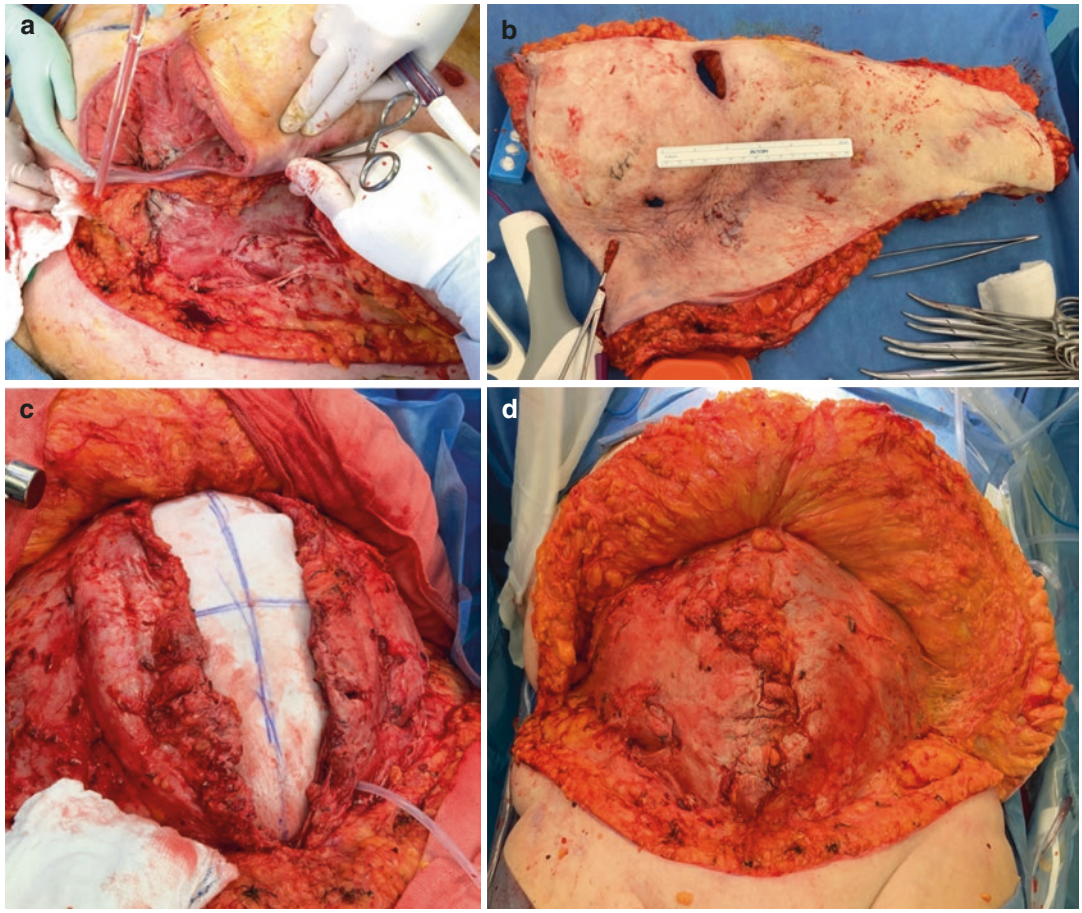

Fig. 3.2 (**a** and **b**) Subsequent abdominoplasty on the patient in Fig. 3.1 followed by (**c** and **d**): posterior component separation and abdominal wall reconstruction with sublay biological mesh

and postoperative complications that arise from primary closure, its use in contaminated or contaminated repairs is controversial [38]. Current VHWG guidelines advise against the use of synthetic mesh when the risk of wound complications is deemed too high [35]. Biological mesh was created to address these concerns. While there have been several case reports on the use of biological mesh in infected fields (with no indication of hernia recurrence at 4–5 years [39]), the evidence in scientific literature requires more time for the results to bear out. As of 2018, there are 21 ongoing randomized trials and observational studies using biological mesh [38]. In our practice, biological mesh had been shown to be effective in elderly patients (age ≥65 years old) undergoing complex abdominal wall reconstruction, with comparable outcomes to non-elderly patients [18].

3.4 Adjunct Procedures in Complex Abdominal Wall Reconstruction

3.4.1 Component Separation

Abdominal wall hernias find their roots with Dr. Albanese who described the first use of component separation technique on a large ventral hernia in 1951 [40, 41]. This technique was eventually popularized into what is now known as the "classic component separation technique." This technique required midline to lateral anterior fasciotomies of the rectus abdominus and release of the external oblique aponeurosis [42]. This release allowed for the coverage of 20 cm wide defects using autologous tissue. The next evolution in component separation arrived with the Rives-Stoppa technique, which was described as a "posterior placement of mesh in a retro rectus fashion" rather than the classic anterior component separation [43]. An additional component of transverse abdominus release, or TAR, was added several years later. It provided additional defect coverage [44]. Since that time, there have been multiple iterations used throughout abdominal wall surgery, including different placements of synthetic or biological mesh, along with the introduction of laparoscopic and robotic approaches to these techniques.

3.4.2 Anterior Component Separation

In the classic anterior component separation technique [35, 38], a midline laparotomy incision is made that encapsulates the hernia. During the anterior component separation (ACS) for abdominal wall reconstruction, dissection and development of the anterior abdominal skin flaps is mobilized laterally from the chest wall to the anterior superior spine. Fascial release is achieved towards the semilunaris, extending towards the ribs and groin. Next, division of the external oblique muscle aponeurosis occurs longitudinally, 2 cm lateral to the lateral edge of the rectus sheath, which will allow the mobilized rectus myofascial component to be brought medially and will facilitate the approximation of the midline with sutures. If the rectus abdominus is unable to be brought together, the internal oblique muscles can be divided bilaterally. Adequate chemical paralyzation is important during this procedure. Moreover, most beneficial will be the separation of oblique muscles (external and internal). Every effort should be made to preserve the skin perforators during dissection in order to create the mucocutaneous flaps. This will greatly reduce skin and subcutaneous necrosis.

Care is given to avoid injury to the internal oblique fascia including the innervations to the rectus muscles. Once the external oblique is

freed, the area created is considered the anterior muscular space. The compound flap containing rectus abdominus, internal oblique, and transversus abdominus is mobilized medially and reapproximated, forming the anterior rectus repair. Synthetic or biological mesh can be used to reinforce this closure and secured using 0 PDS sutures. It must be ensured that onlay (very rarely used) or inlay mesh covers the newly made space, and sutures should extend past the dissection and incorporate the borders of the dissected plane.

3.4.3 Posterior Component Separation With/Without Transversus Abdominis Release (TAR)

The open posterior component separation technique begins with a midline laparotomy incision. The retromuscular space is created by incising the posterior rectus sheath and releasing the rectus muscle. The lateral dissection can continue by dividing the posterior aponeurotic sheath of the internal oblique muscle [37]. Doing so will allow access to the plane between the transversus abdominis and internal oblique.

Posterior component separation (PCS), with or without transversus abdominus release (TAR), has become popular for large midline hernias, particularly with loss of abdominal wall domain, and has become a technique of choice for complex abdominal wall reconstruction (CAWR) for many of us for several reasons. These are mainly because of advances in surgical techniques and the reduction of skin and subcutaneous complications. The main principles of PCS are the sparing of the neurovascular bundle and mesh placement posterior to the rectus muscle in a sublay position.

Once the lysis of adhesions and other concomitant procedures, such as reconstitution of the GI tract, are completed, PCS can begin by incising the medial edge of the posterior rectus sheath 1 cm lateral to the linea alba. The edge of the transected posterior rectus sheath is grasped with clamps and retracted medially and posteriorly, while the rectus muscle is gently elevated anteriorly, allowing easy lateral dissection of the retrorectus space (Fig. 3.3). During this stage of the operation, the surgeon must be cognizant in preserving the neurovascular bundle. The multiple perforators and the epigastric vessel (superiorly and inferiorly) are fragile vessels that can be easily injured at any stage of the operation.

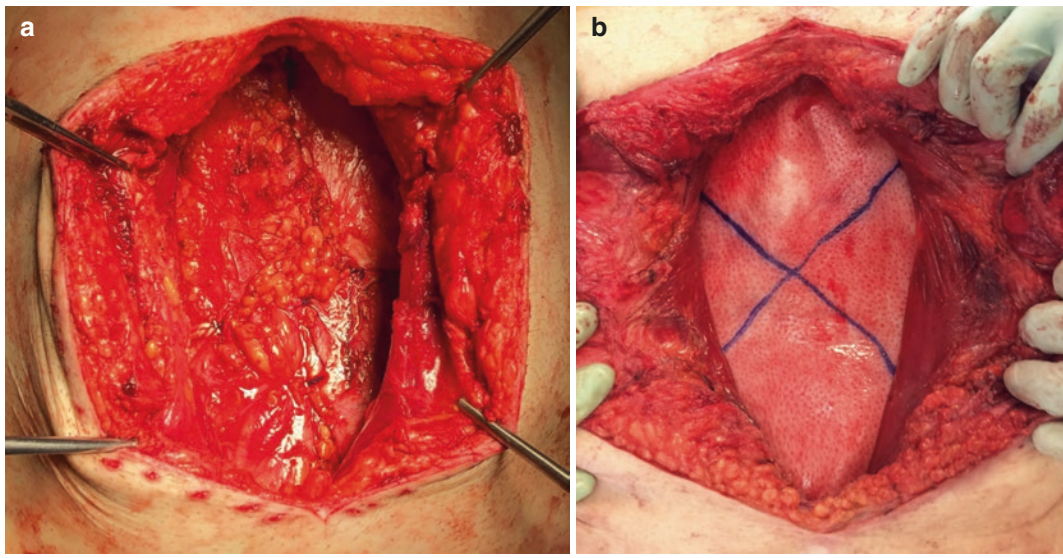

Fig. 3.3 (**a**) Posterior component separation—Kocher clamps on the rectus abdominus muscles with the posterior rectus sheath reapproximated. (**b**) Biological mesh placed in a sublay fashion (posterior to the rectus abdominus)

The posterior lamina of the internal oblique aponeurosis is incised just medial to the entry of the intercostal nerves as they enter the rectus muscle posteriorly. Dissection of this segment should begin as cranially as possible.

In cases of post liver transplant hernias, it does not make much sense to try to separate the liver from the posterior rectus sheath (PRS) and risk entering the liver during the dissection. Instead, the preferred procedure is to drop the PCS together with the liver, in order to create the space for it should be possible to see the medial aspect of the transversus abdominus muscle (TAM). The muscle fibers and fascia of TAM can be separated from the underlying thin posterior transversus abdominis fascia and peritoneum with a right-angle clamp. However, this separation requires a careful dissection under the muscle fibers of TAM. One has to be careful not to enter the peritoneum. If this occurs, the defect must be identified and immediately closed with absorbable suture. We prefer to conduct this portion of the operation sharply (with electrocautery or scissors), but always under direct vision. Blunt dissection should be avoided as it may cause bleeding. Once the space is satisfactorily created, the posterior rectus sheaths are approximated with running absorbable suture (0-Vicryl). At this stage, the mesh size is fashioned according to the size of the space, but it must be ensured that the mesh (irrespective of what kind) is not folded in on itself. Fixation of the mesh superiorly, inferiorly, and laterally with sutures will help position the mesh appropriately (Fig. 3.3). Several techniques can be used to place the sutures. We refer to use a Carter-Thomason suture passer, but other suture passers are adequate to fix the mesh to the anterior abdominal wall.

At our institution, we have an ongoing prospective observational study examining the technique of open complex abdominal wall reconstruction using porcine-derived acellular matrix (Strattice™). Initial placement of the biological mesh was used in the underlay (intraperitoneal) position using anterior component separation. However, since 2017, our group has gradually changed to using a posterior component separation approach with or without transversus abdominus muscle release. Mesh placement has also changed to the sublay (retrorectus) position. Our approach incorporates the sparring of all neurovascular bundles, and the linea alba is closed over the mesh whenever possible. We also place two or three 19-French Blake drains below the fascia-adipocutaneous flaps to prevent the risk of seroma formation [18].

3.5 Conclusion

There have been major advances in abdominal wall surgery. Fundamental knowledge of abdominal wall surgery and a plethora of well-defined prophylactic surgical techniques are now widely recognized and employed, with each having its own learning curve. The prophylactic approaches are useful while dealing with complex reoperative cases, and hernia surgeons should decide wisely based on their own experience guided by scientific evidence. In high-risk patients, there should be a prophylactic mesh placement.

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4 Cost-Effectiveness of Prophylactic Surgeries in Preventing Hereditary Predisposition Syndromes

Charles Sabbagh

4.1 Introduction

The aim of cost-effectiveness analysis is to evaluate the cost and health benefit of one strategy compared to another. It helps to define and illuminate the potential health benefits lost when the best alternative is not selected [1, 2]. Cost-effectiveness analysis should include both a societal and healthcare sector perspective. One of the easier methods to evaluate cost-effectiveness is to evaluate the cost-per-quality–adjusted life-year (QALY) [1].

Cost-effectiveness analysis can be useful in hereditary syndromes in the decision of surveillance versus prophylactic surgery. Cost-effectiveness has mainly been evaluated in Lynch syndrome and BRCA1 syndrome.

4.2 Lynch Syndrome

4.2.1 Prophylactic Surgery in Lynch Syndrome

There are three types of prophylactic surgery for Lynch syndrome (LS) [3]. The first is primary prophylactic surgery. There are no formal indications for primary prophylactic colorectal surgery in LS, as prophylactic colorectal surgery is not recommended when the patient is free from colonic lesions [4]. Total carcinological colectomy at the age of 25 has been predicted to increase survival by 1.8 years compared to endoscopic surveillance [5]. The lack of an indication explains the lack of cost-effectiveness data for prophylactic colorectal surgery in LS in the field of primary prophylactic surgery.

Primary prophylactic colon surgery can be proposed for LS patients with endometrial cancer (EC) requiring a hysterectomy without preservation of the adnexa. Indeed, EC is often referred to as a "sentinel event" in females with LS because it is the first manifestation of LS in more than one in two women [6], with an earlier age of onset than in sporadic EC [6]. EC in LS occurs significantly more commonly in patients with early menarche, nulliparity, and short-term or no oral contraception (1 year) [7]. Women with LS who develop EC have an increased risk of developing colorectal cancer. Thus, according to a previous study based on the Amsterdam criteria, Aarnio et al. (2015) found that the collective risk (CR) of colorectal cancer 26 years after the development of EC ranged from 40 to 75% [8]. According to a recent registry study that included 127 LS patients with EC, 55% (n = 70) developed a second cancer, more than half (n = 40) of which were colorectal cancer. Indeed, LS women with EC have a 40-fold higher risk of develop-

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ing colorectal cancer than women of the general population [9], which could be the basis for discussion of prophylactic colectomy at the time of total hysterectomy.

The question of primary prophylactic surgery in LS is mainly in the context of gynecological tumors. Given the risk of EC (narrow spectrum) and ovarian cancer (wide spectrum), gynecological examinations and pelvic ultrasound, with measurement of the endometrial thickness, are recommended every year after age 35 or starting 5 years before the first case of EC in the family. Prophylactic surgery (total hysterectomy with bilateral salpingo-oophorectomy) should be discussed starting at age 45 or 5 years before the first case of EC in the family.

The second type of prophylactic surgery is secondary prophylactic surgery. Most surgical indications for LS are therefore based on the treatment of either a colorectal cancer or an endoscopically unresectable dysplasia or adenoma. Either segmental or total colectomy can be proposed, depending on the location of the lesion. For rectal lesions, a proctectomy, with or without sphincter preservation, or total coloproctectomy can be discussed. In addition to location, the choice of the technique must take into account patient factors (age, comorbidities, personal choice), the morbidity of the procedure, the functional sequelae engendered, the impact on the quality of life, and, finally, the risk of developing a metachronous lesion. These considerations are necessary to provide patients with the most complete information. This decision can be difficult to make and cost-effectiveness analysis can be useful in such situations.

4.2.2 Cost-Effectiveness Studies in Lynch Syndrome

Several series have evaluated the best prevention strategies for gynecological cancers in LS. In 2008, Kwon et al. developed a Markov decision-analytic model to estimate the best strategies in a cohort of women with LS at risk of endometrial and ovarian cancer [10]. The authors compared five strategies: no prevention; prophylactic surgery (hysterectomy and bilateral salpingo-oophorectomy) at the age of 30 years; prophylactic surgery at the age of 40; annual screening with endometrial biopsy, transvaginal ultrasound, and CA125 from the age of 30; and finally, annual screening from the age of 30 until prophylactic surgery at the age of 40 (defined as the combined strategy). The authors measured the QALY and incremental cost-effectiveness ratio (ICER). They found that the combined strategy provided the highest net health benefit (18.98 QALYs) but had an ICER of $194,650 per QALY relative to prophylactic surgery at age 40 (the second-best strategy). The authors finally found that the combined strategy was the most effective gynecological cancer strategy [10]. In 2011, Yang et al. published another cost-effectiveness analysis of prophylactic surgery versus gynecological surveillance for women with LS [11]. The authors also designed a decision-analytic model incorporating key clinical decisions and existing probabilities, costs, and outcomes from the literature. The aim of this study was quite different from that of Kwon et al. (2008), as in this study, the authors compared the health outcomes of prophylactic hysterectomy with bilateral salpingo-oophorectomy at age 30 versus annual gynecological screening, versus annual gynecological examinations [11]. The authors found that risk-reducing surgery was the least expensive option, with a cost of $23,422 per patient for 25.71 QALYs, whereas annual screening costs $ 68,392 for 25.17 QALYs, and annual examination without screening, $100,484 for 24.6 QALYs. The conclusion was in favor of prophylactic surgery, as it leads to the lowest cost and the highest number of QALYs. The main limitation of this study was that it only included one age for prophylactic surgery. The decision-analytical model was also a limitation relative to a prospective trial with real women but is inherent to this specific methodology.

As already mentioned, there is no indication of primary colonic prophylactic surgery but there is an indication for secondary prophylactic surgery and the main question for which cost-effectiveness analysis could be useful is whether to perform a segmental or total colectomy. In 2019, Jiang et al. published a cost-effectiveness

analysis of total colectomy versus segmental colectomy [12]. The authors performed a Markov decision tree analysis and compared QALYs following total colectomy or segmental colectomy. The authors obtained the probabilities, cost, and utility from the literature. In the base case analysis, a single total colectomy saved 0.67 QALY, at a cost of $ 17,925 per patient. This led to an incremental cost-effectiveness ratio of $ 26,624/QALY for patients undergoing a total colectomy [12]. Earlier studies have been published on this topic. In 2010, Maeda et al. published a Markov model-based study and found that mean survival was slightly better for total than segmental colectomy for patients younger than 30 years of age. However, the two strategies were approximately equivalent when QALY was considered, with 21.2 QALYs per patient for total colectomy and 21.5 for segmental colectomy [13]. Nonetheless, the study by Jiang et al. (2019) is the first to show not only the improvement in life expectancy but also the cost-effectiveness of total colectomy over segmental colectomy [12].

4.3 Familial Adenomatous Polyposis

Patients with familial adenomatous polyposis can have several hundreds or even thousands of colorectal polyps, starting during adolescence and leading to an inevitable risk of colorectal cancer before the age of 40. These patients can also develop duodenal adenomas with a 300-fold higher risk of developing duodenal adenocarcinoma than the general population [14]. The severity of duodenal adenomas is currently evaluated using the Spiegelman classification. In 2017, Sourrouille et al. evaluated the Spiegelman duodenal surveillance score, in particular with respect to high-grade dysplasia. Multivariable analysis found that age at the first endoscopy and modifications of the papilla (size and gross aspect) were independent risk factors associated with high-grade dysplasia [15]. It is therefore necessary to evaluate the gross aspect of the papilla to appreciate the risk of duodenal dysplasia. Moreover, desmoid tumors occur in 10–15% of cases at a median age of 30 years and are the leading cause of mortality in patients with familial adenomatous polyposis after prophylactic colorectal surgery [16]. Desmoid tumors are mesenchymal tumors. They occur preferentially within the abdomen and are benign (no risk of metastasis) but are life-threatening because of their potential for locoregional complications. Other types of tumors are rare (1–2% of patients) and include hepatoblastoma (in boys between 6 months and 3 years of age), cerebral tumors in children or adolescents (mainly medulloblastoma, formerly known as Turcot syndrome), papillary cancer of the thyroid, and pancreatic cancer. Other possible lesions are glandular-cystic gastric polyps, which occur frequently and are benign, and even gastric adenomas and extra-digestive benign lesions, which are less frequent but herald the occurrence of colorectal adenomatous polyps, as well as dental anomalies (supernumerary or sunken teeth, maxillary osteoma), asymptomatic hypertrophy of the retinal pigmented epithelium, and skin lesions (epidermoid cysts, lipoma).

4.3.1 Cost-Effectiveness in Familial Adenomatous Polyposis

In familial adenomatous polyposis, the goal of prophylactic surgical treatment is to prevent death related to colorectal cancer without affecting the quality of life. Of note, one of every four patients have colorectal cancer at the time of the operation and one of three develop rectal cancer during the postoperative surveillance period [17]. There are currently no standardized guidelines or consensus as to when to operate or which procedure to perform [18]. However, in 2009, the French National Institution of Cancer (INCA) published professional recommendations for prophylactic surgery for patients with a genetic predisposition for cancer, and in 2017, the French High Health Authority published recommendations concerning screening and prevention for high and very high-risk patients. In these recommendations, age, as well as the size, number, and histology of the polyps, should figure in the indication for prophylactic surgery. In the absence of

polyps >5 mm and/or those with a villous component, and/or high-grade dysplasia, surgery can be deferred. Endoscopic surveillance is therefore fundamental. In certain cases, surgery can be deferred because of the higher risk of desmoid tumors than that of colorectal degeneration. In a recent meta-analysis [19] that included 4625 patients, multivariable analysis found that an age of under 40, family history, mutations in the APC gene 3′ of codon 1399, a previous laparotomy, and female gender were independent risk factors for developing a desmoid tumor (n = 559, i.e., 12%). The authors suggested deferring prophylactic colorectal surgery to limit the risk of onset of desmoid tumors, in particular in women with attenuated FAP characterized by a mutation of the APC gene 3′ of codon 1399.

Several elements in the field of colorectal management could be evaluated by a cost-effectiveness analysis, including the age of resection and the type of resection according to the type of mutation or surgery in MUTYH patients. However, there are no currently (June 2020) published cost-effectiveness studies in the field of prophylactic colorectal surgery for familial adenomatous polyposis.

In 2009, Greenblatt et al. published a cost-effectiveness study of prophylactic surgery for duodenal cancer. A Markov model was constructed to estimate the life expectancy and cost of three strategies: pancreaticoduodenectomy at Spigelman stage III, pancreaticoduodenectomy at Spigelman stage IV, and pancreaticoduodenectomy at cancer diagnosis. The authors simulated a cohort of 30-year-old familial adenomatous polyposis patients with total colectomies until age 80. They found that prophylactic surgery at Spigelman stage IV resulted in the greatest life expectancy. They also found that surgery at Spigelman stage IV was more expensive than surgery at cancer diagnosis, with an increased cost of $3200 per QALY gained. The authors also found that surgery at Spigelman stage III was not a valid option. This is, up to now, the only cost-effectiveness study on prophylactic surgery in familial adenomatous polyposis [20].

4.4 Hereditary Breast Cancer

4.4.1 Mutation BRCA1/BRAC2

In 2017, recommendations were published by the *Institut National du Cancer* on prophylactic surgery in patients with a BRCA1/2 mutation.

Prophylactic bilateral mastectomy was considered to be the most effective means to prevent breast cancer for patients without breast cancer with a BRCA1/2 mutation, despite its mutilating nature. Bilateral mastectomy should thus be among the proposed treatments for women free of cancer with a BRCA1/2 mutation. Whether to proceed with the surgery is the personal decision of the patient after the issues have been presented by an oncogeneticist and a surgeon and a minimum cooling-off period. Performance of the surgery is not considered to be urgent. A consultation with a psychologist should be systematically offered to patients as part of this procedure. The choice of preventive mastectomy must be approved before it is performed by an oncogenetics multidisciplinary team (MDT). However, it is not intended that the MDT proposes one treatment strategy over another. Rather, the responsibility of specialized MDTs is the treatment and follow-up of the women who choose risk-reduction surgery. The breast cancer risk-reduction surgery itself must be carried out by surgeons specializing in cancer treatment (expert opinion). Patients who do not choose this option should also be informed that they may be able to reconsider their choice at a later date. Current data do not allow determination of the optimal age at which bilateral mastectomy should be performed. However, given the rarity of breast cancer before the age of 30, it is not appropriate to offer this procedure before that age, except in cases of very early-onset breast cancer in the family. There is no data to specify the age beyond which the performance of a bilateral mastectomy would not provide a survival gain. However, over the age of 65, the benefit–risk balance of a breast cancer risk-reduction surgical strategy should be evaluated on a case-by-case basis (expert opinion).

Risk-reduction breast surgery (bi-mastectomy or contralateral) should be proposed to patients treated for breast cancer. The clinical relevance must always be balanced with the cancer prognosis, in particular the probability of progression of the first cancer within 3–5 years. Such surgery is not considered to be urgent within the context of the breast cancer treatment. In cases of cancer with a poor prognosis, especially if there is a risk of rapid progression within 3–5 years, it is recommended to not consider risk-reduction surgery but to wait to ensure that the cancer does not develop rapidly. It should be noted that, given the prognosis of adnexal cancer (ovaries and tubes), breast cancer risk-reduction surgery is not recommended for patients who have had adnexal cancer within the previous 5 years.

For the risk of ovarian cancer, adnexectomy is the recommended risk-reduction strategy for women with a BRCA mutation who are free of breast cancer and/or adnexal cancer, given its proven efficacy in reducing the risk of adnexal cancer and its benefit for survival. The optimal minimum age cannot be determined and specific issues need to be considered, in particular, pregnancy and the consequences of hormonal deprivation.

Adnexectomy is recommended as early as the age of 40 for women without adnexal cancer, regardless of the BRCA mutation status. This intervention can be delayed until the age of 45 for women with BRCA2 mutations. The minimum age can be rediscussed with patients in specific cases, such as the occurrence of adnexal cancer at an earlier age or if the woman requests it.

Several cost-effectiveness studies have been published concerning prophylactic surgery in BRAC1/2 women. In 2018, Petelin et al. published a systematic review covering cost-effectiveness and comparative effectiveness of cancer risk management strategies in BRAC1/2 mutation carriers. A total of 26 economic evaluations and eight comparative effectiveness analyses were included in this study [21]. The biggest challenge in BRAC1/2 evaluation is that several situations must be evaluated, such as the risk of breast and/or ovarian cancer for women with or without cancer and those who are confirmed or potential BRCA carriers.

For confirmed BRCA carriers, the authors concluded that risk-reducing salpingo-oophorectomy and bilateral prophylactic mastectomy were the strategies associated with the greatest increase in life expectancy and the dominant strategy in terms of cost-effectiveness. This strategy leads to an increase in life expectancy ranging from 0.62 to 9 life years gained relative to other strategies (no intervention or cancer screening). Moreover, inclusion of the adverse effects related to risk-reducing salpingo-oophorectomy–induced premature surgical menopause did not appear to affect the results [21].

Among these studies, one concerned a cost-utility analysis of risk-reducing bilateral salpingectomy, with or without delayed oophorectomy, as a possible alternative to risk-reducing salpingo-oophorectomy, as this approach has been suggested to minimize the potential long-term adverse effects associated with early risk-reducing salpingo-oophorectomy [22]. Salpingectomy alone and salpingectomy with delayed oophorectomy were considered cost-effective alternatives for BRCA1 carriers, with a cost of $17,003 to $32,126 per QALY gained. They were potentially cost-effective for BRCA2 carriers, with a cost of $21,779 to $76,992 per QALY gained. Cost-effectiveness was highly sensitive to the inutility assigned to salpingectomy.

For confirmed BRCA carriers with breast cancer, contralateral prophylactic mastectomy, with or without risk-reducing salpingo-oophorectomy, was the most effective strategy for the management of secondary breast cancer risk in terms of life years gained, QALYs, and cost-savings relative to breast cancer screening.

For confirmed BRCA carriers with ovarian cancer, bilateral prophylactic mastectomy was only cost-effective for patients from 40 to 50 years of age who were BRCA1 carriers [23].

4.5 Conclusion

Cost-effectiveness analyses are useful for prophylactic surgery indications to optimize the indications, the type of surgery, and the best moment to perform the surgery. However, the available data is still limited.

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Prophylactic Thyroidectomy

5

Xiang Da Dong and Rifat Latifi

5.1 Introduction

Cancer is currently the second most common cause of death in the United States [1]. A subset of cancers is caused by the presence of genetic defects leading to instability in the genome [2]. Many hereditary malignancies have been identified through genetic sequencing and linked to particular coexisting conditions. Knowing that certain hereditary cancers have a high rate of penetrance, precautionary measures are needed to mitigate either the mortality associated with a disease or the morbidity caused by the disease [2]. In the twenty centuries, the morbidity and mortality of surgical procedures have been reduced dramatically due to advances in surgical techniques and perioperative care, as well as other medical advances. Therefore, many prophylactic surgeries are being performed to reduce the incidence of organ-specific diseases when the morbidity of surgery is acceptable. Total thyroidectomy represents one of the models for prophylactic surgery to mitigate the development of surgically treatable thyroid diseases.

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In order to proceed with prophylactic operations, several criteria should be met. The knowledge that the predisposing condition warrants intervention due to risk of cancer development or significant morbidity with age need to be confirmed through preoperative workup and genetic testing. Ideally, a quantifiable risk category needs to be given following the workup. The tests to determine the population most at risk should be reproducible and readily available. The ability to perform the surgery with minimal morbidity and mortality is a prerequisite for surgery. On occasion, organ function replacement with exogenous medications is needed such as the case for post thyroidectomy state. Finally, patients need to be followed to look for evidence of recurrent disease [2].

The thyroid gland is one of the organs that can be safely removed for the purpose of treating cancer with proper hormone replacement afterwards. Following discovery of thyroxine, thyroidectomy was attempted initially with variable results. Currently, thyroidectomy can be performed with minimal morbidity in expert hands. Therefore, several conditions that can cause thyroid cancers would lead one to consider the possibility of thyroidectomy to minimize cancer development [3–6]. In terms of thyroidectomy, this has been routinely used in MEN2A, MEN2B, and other types of familial MTCs (FMTC) due to the RET proto-oncogene defect [7]. This is a particularly worrisome cancer that can be effectively treated with prophylactic surgery. However, there

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are other genetic conditions such as Cowden syndrome which can cause less aggressive differentiated thyroid cancers (DTC). Although prophylactic surgery offers significant protective effect, the benefits and risks of surgery need to be weighed prior to intervention. Furthermore, surveillance of thyroid gland for neoplasia is oftentimes easily reproducible without morbidity.

Barriers to the routine performance of prophylactic thyroidectomy are numerous. Availability of surgical expertise is one of the first barriers. Identification of patients at risk based on genetic lineage is another. Determining the timing of surgery in pediatric patients will be important as the patients are at increased risk of surgical complications compared to adults. Furthermore, the group of patients most at risk for development of cancer is also the group least capable of making informed decisions for themselves. Finally, one of the benefits of the Human Genome Project has been development of pharmacologic agents capable of specific blockade of metabolic pathways [8]. The development of newer agents capable of inhibiting the genetic development of cancer is only now being investigated and may render prophylactic surgeries obsolete in the future.

In this review, we will examine the role of prophylactic thyroidectomy for a variety of conditions that may trigger cancers in patients. The various genetic predispositions are examined in detail in terms of their particular risks. In addition, the age and benefit to the patient will be evaluated for the long-term morbidity and benefit ratio. Consequences of the surgery will be discussed for the patients. Finally, benign conditions that are not routinely indicated for thyroid surgery are touched upon as well.

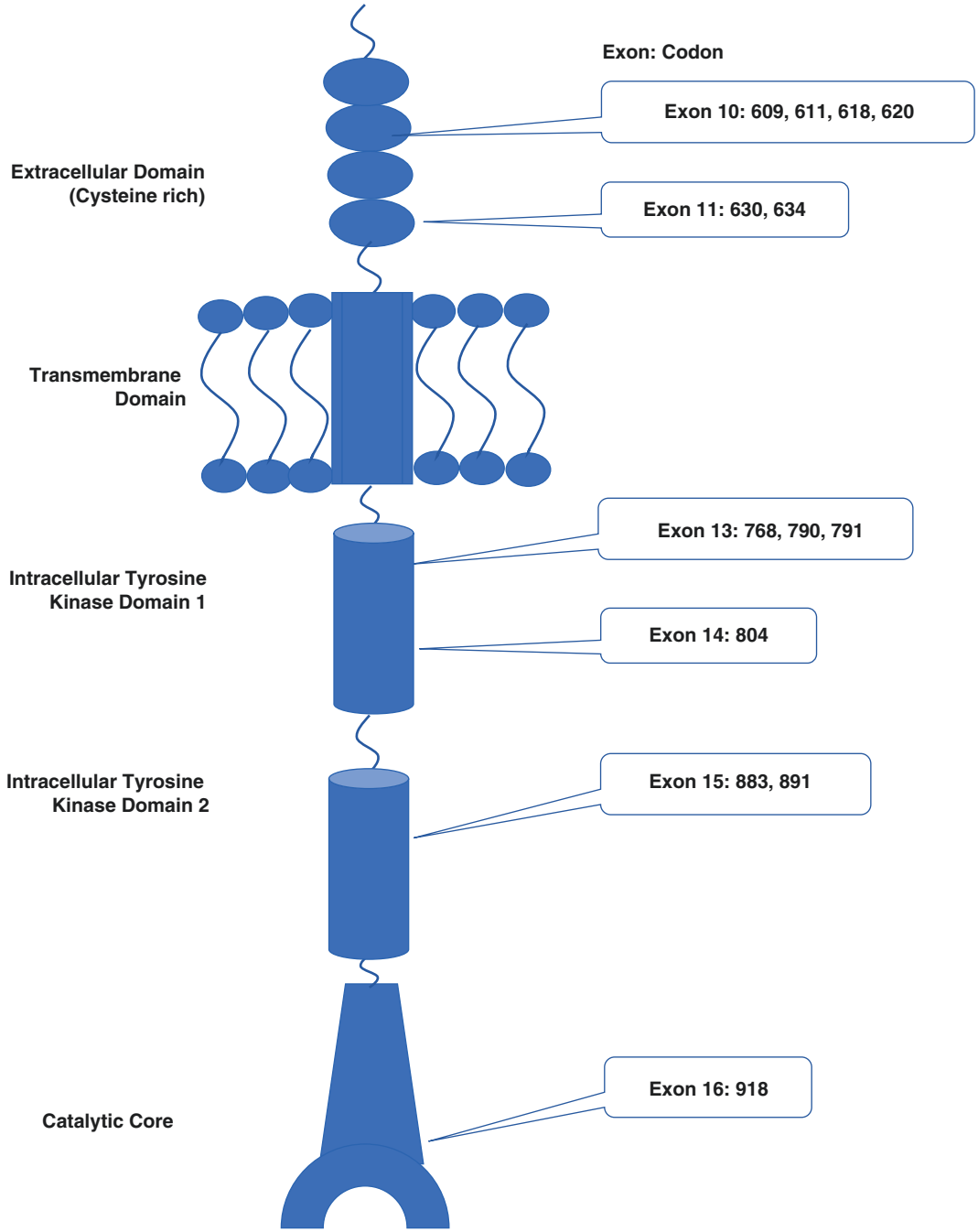
5.2 Familial Medullary Thyroid Cancer

One of the fundamental requirements for prophylactic surgery is the identification of at-risk patients. This process of identifying at-risk individuals requires germline testing to ensure that the risk is present prior to the choice of selecting prophylactic surgery to reduce the risk of malignancy [9]. Approximately 5–10% of thyroid cancers are MTCs and over 25% of these are related to hereditary RET gene defect as part of three autosomal dominant disorders: MEN2A, MEN2B, and familial FMTC. MTC is a rare type of neuroendocrine tumor that arises from parafollicular C cells of the thyroid gland. Surgery in these patients offers a particularly effective means to control and cure a potentially fatal malignancy. Unlike colorectal or breast cancers, there are also no chemotherapeutic means to prevent the development of MTCs. Furthermore, effective means of detecting precancerous lesions may not be easily achievable such as in infants with MEN2B disease. Therefore, prophylactic thyroidectomy remains the cornerstone of surgical prophylaxis in these patients.

5.2.1 RET Proto-Oncogene

The RET proto-oncogene was first identified in 1985 and found to be a transmembrane tyrosine kinase receptor [9–13]. This gene was localized to the pericentriomeric region of chromosome 10 (locus 10q11.2) and subsequently referred to as RET (Rearranged during Transfection) proto-oncogene [10, 12, 13]. The RET protein is a tyrosine kinase (TK) receptor that affects growth and differentiation. The protein comprises an extracellular domain with both cadherin-like and cysteine-rich regions. Within the intracellular components, two tyrosine kinase subdomains are present. Binding of the ligand to the receptor leads to RET dimerization and subsequent intracellular substrate phosphorylation (Fig. 5.1) [10].

The RET proto-oncogene is a gain of function protein and mutations can lead to oncogenesis of thyroid parafollicular C cells [14–16]. More than 100 RET mutations have been reported to date [14–16]. The specific RET mutation also has a direct correlation with the phenotype and



Codon 883 and 918 associated with MEN 2B. All others are associated with MEN 2A and FMTC.

Fig. 5.1 Schematic diagram of RET proto-oncogene along with the associated exon and codon defect

aggressiveness of the MTC and other features of the MEN syndrome. RET protein itself has four ligands including artemin, persephin, neurturin, and glial cell line-derived neurotrophic factor [14–16]. Binding of the ligand leads to subsequent intracellular dimerization. Alternatively, when there is a germline mutation, the intracellular tyrosine kinase can be constitutively activated.

Mutations in the extracellular domains of RET frequently is associated with FMTC and MEN2A. Occasionally, FMTC is considered a subtype of MEN2A. MEN2A has been subclassified into four variants and includes classic MEN2A, MEN2A with cutaneous lichen amyloidosis, MEN2A with Hirschsprung's disease, and FMTC [17]. Testing for children who display phenotypic findings of either MEN2A or MEN2B should have directed testing of the most common mutations first followed by less common mutations, and subsequent gene sequencing if needed. The follow-up care for patients following identification of their mutation will depend on the mutation itself. In patients with suspected MEN2A, the vast majority of patients have a missense mutation in the extracellular domain at a single codon [14]. Exons 10 and 11, with codon mutations in 609, 611, 618, 620, 630, and 634, represent the most common types of mutations [7]. Codon 634 mutation in exon 11 is also the most common gene variant in MEN2A and is found in the majority of patients with classic-type MEN2A [18, 19]. Interestingly, somatic RET mutations that occur with sporadic MTC, which occurs in 75% of cases, also typically occur in exon 11 at codon 634. Sporadic MTC, although they can present at any age, is usually later in onset and presents with presence of thyroid mass and presence of concurrent nodal metastases [9, 20].

When the intracellular TK domains of the RET gene is involved, development of MTC is usually earlier in onset although such mutations are much less common [21]. The intracellular TK2 domain mutation on exon 16 (codon 918) is responsible for 95% of MEN2B cases, followed by exon 15 (codon 883) [16, 21]. These deeper intracellular mutations often lead to aggressive early-onset tumors that mandate management early on. Following identification of patients with any MTC, all patients should be screened for familial patterns of inheritance. Newly diagnosed FMTC should also prompt dissemination of information to related kindreds due to the high penetrance of cancer (Table 5.1).

5.2.2 Current ATA Recommendations for Screening and Prophylactic Thyroidectomy

Patients with newly diagnosed MTC or C cell hyperplasia frequently require next-generation sequencing of exons 10, 11, 13, 14, 15, and 16 in order to ascertain their risks both for MTC and other associated malignancies seen with MEN syndromes. Once an index patient has been diagnosed with a germline RET mutation, it is also imperative that their first-degree relatives be offered the opportunity to evaluate for the presence of MEN or FMTC syndrome.

Current American Thyroid Association (ATA) guidelines list the recommended age of surgery for patients based on the risks of MTC development with the particular types of mutation (Table 5.2).

Table 5.1 Risk of medullary thyroid cancer development based on hereditary condition

Type	Thyroid distribution	Familial pattern	Associated clinical abnormalities	Biological aggressiveness
MEN 2A	Bilateral	Yes	Pheochromocytoma, hyperparathyroidism	2+
MEN 2B	Bilateral	Yes/no	Pheochromocytoma, neurofibromatosis	4+
Familial MTC	Bilateral	Yes	None	1+
Sporadic	Unilateral	No	None	3+

Table 5.2 Timing of surgery based on RET mutation based on 1999 consensus statement from the Seventh International Workshop on Multiple Endocrine Neoplasia

Risk level	RET mutation codons	Timing of RET testing	Timing of first serum calcitonin testing	Timing of first US	Recommended surgery age
A	609, 630, 768, 790, 791, 804, 891	<3–5 years	>3–5 years	>3–5 years	Before 5–10 years of age
B	609, 611, 618, 620, 630	<3–5 years	>3–5 years	>3–5 years	Consider surgery before age 5 years; may be delayed beyond age 5 years if criteria met
C	634	<3–5 years	>3–5 years	>3–5 years	Before 5 years of age
D	883, 918, 922	<1 year	≥6 months if surgery delayed	<1 year	<1 year

As the presence of RET gene defect leads to near 100% certainty of MTC, the only question is the timing prophylactic surgery balancing the risk of surgery on patients with the risk of developing malignancies. Both prospective and retrospective data comparing the use of positive DNA testing for RET versus serum biochemical evaluation with calcitonin levels have shown that DNA testing leads to predictable and more accurate risk assessment for patients [9]. Studies have shown that patients undergoing thyroidectomy for increased calcitonin levels were older than those undergoing surgery for positive DNA testing [18, 21]. Similarly, the risk of medullary thyroid cancer is much higher in those who already have elevated levels of calcitonin in their blood [18, 21]. The timing of surgery therefore should predate the rise in serum calcitonin and presence of thyroid nodules based on ultrasonographic evaluations.

Following diagnosis of MTC based on fine needle aspiration in an index patient or from a patient following confirmation of genetic heritage, patients will need either screening or surgical intervention. In patients with MEN II syndromes, associated endocrinopathies such as pheochromocytoma and hyperparathyroidism need to be excluded or evaluated to minimize the risk of concurrent disease. Those patients undergo screening with either plasma-free metanephrines or 24-h urine collection for metanephrines to rule out pheochromocytoma which can increase the risk of thyroidectomy if not previously discovered. Presence of hyperparathyroidism also needs to be confirmed because of the need to alter surgical plan to possibly include parathyroidectomy concurrently. Patients with delayed surgical intervention should have serum calcitonin and CEA levels checked along with periodic thyroid ultrasonography to evaluate for presence of thyroid nodules. In patients with RET proto-oncogene defect, the screening for pheochromocytoma should commence by 11 years of age in highest risk individuals (MEN2B).

Once the RET gene defect has been identified, clear-cut ATA guidelines exist regarding the timing of surgery since risk of MTC development increases incrementally (Fig. 5.2). For patients with FMTC and MEN2A, RET codon defects such as 609, 630, 768, 790, 791, 804, 891 should undergo screening evaluation and possible prophylactic thyroidectomy before the age of 10. Children with codon defects including 609, 611, 618, 620, 630 need to consider surgery by 5 years of age. Those with codon 634 defect is the most common type of MEN2A and also at particularly increased risk of malignancy. Therefore, patients with codon 634 defect need to undergo surgery by 5 years of old. Finally, patients with MEN2B are at the highest risk for MTC. Surgery should not be postponed much beyond 1 year of age in these high-risk individuals, even with the elevated risk of surgical morbidity [9, 22–24].

5.3 Cowden Syndrome/PTEN Hamartoma Tumor Syndrome

Cowden syndrome, named after the patient of the same last name, was first described in 1962 [25]. This syndrome was described in a patient with

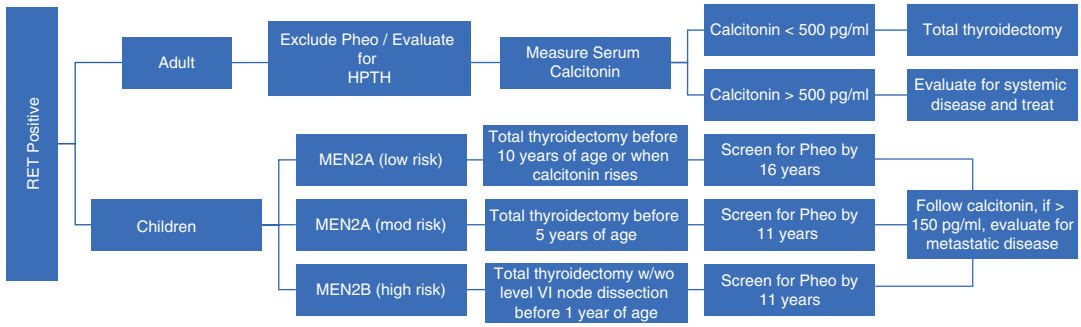


Fig. 5.2 Schematic workup following identification of RET proto-oncogene defect

findings of multinodular goiter, papillomas of the oral mucosa, cystic breast diseases, and CNS abnormalities. Patients of this syndrome seem to have a familial pattern of inheritance. Subsequent investigations into this cluster of syndromes led to the identification of other findings commonly seen with Cowden syndrome [26–29]. Patients often have concurrent trichilemmomas, acral keratoses, and fibromas. The phenotypic abnormalities did not end with its early description. Other unusual findings in some patients with Cowden syndrome included Lhermitte–Duclos disease with its phenotypic dysplastic cerebellar gangliocytoma and gastrointestinal hamartomas. During the 1990s, genetic linkage studies were able to identify a tumor suppressor gene, phosphatase and tensin homolog gene (PTEN), as possible cause for up to 80% of patients developing the constellation of findings [26, 30]. With this finding, another group of patients were also found to have PTEN mutations but other phenotypic appearances. Patient with Bannayan–Riley–Ruvalcaba syndrome was found to have PTEN gene defect in up to 60% of patients. These patients have early-onset macrocephaly, gastrointestinal hamartomas, vascular malformations, Hashimoto's thyroiditis, and penile freckling [27–29, 31]. Patients with either somatic or hereditary PTEN mutations are associated with breast, thyroid, renal, endometrial, colorectal, and melanoma-type malignancies.

Subsequently, with increasing recognition, patients with PTEN hamartoma tumor syndromes are diagnosed based on clinical criteria developed by the International Cowden Consortium [4, 5]. Patients with Cowden syndrome with underlying germline PTEN mutations are at increased risk of breast, thyroid, endometrial, and renal cancers. The majority of patients with Cowden syndrome are diagnosed in a de novo fashion. Following discovery of their first malignancy, the development of secondary malignancy is reportedly as high as 40%, in comparison to about 18% in the general population [32].

Initial presentation of a new patient with PTEN hamartoma syndrome can be quite difficult to recognize due to diverse clinical presentations. However, since secondary cancer risk is elevated compared with normal population, it is important to identify this group of patients following initial workup because of their risk for developing another malignancy. Several features of patients with PTEN hamartoma syndrome that are rare in the general population include the following: (1) Lhermitte–Duclos disease (dysplastic cerebellar gangliocytoma), (2) extreme macrocephaly, (3) oral mucosal papillomatosis, (4) penile freckling, (5) hamartomas and ganglioneuromas of the gastrointestinal tract, (6) glycogenic acanthosis, (7) differentiated thyroid cancer in pediatric patients, and (8) early-onset endometrial cancer [25, 31–33].

Because of the increased recognition of this underreported disease, there is now the Cleveland Clinic PTEN risk calculation tool which can help determine a percentage risk for PTEN mutation analysis. Patients with high-risk scores will need genetic counseling and testing. Identification of patients with PTEN gene defect should alert the clinician to increased scrutiny and testing

of patients [32, 34]. Additionally, prior cancer in these patients increases the risk of secondary cancers in patients with PTEN hamartoma syndrome. Therefore, these patients may benefit from prophylactic surgeries or therapeutic interventions [32].

The lifetime risk of patients with germline PTEN mutation for development of malignancies is high. Collectively, based on several studies, the risk of female breast cancer ranges from 67 to 85% [33]. Risk of DTCs is lower but ranges from 25 to 38%. Similar to breast cancer, the risk is higher in women for thyroid cancer than men [33]. Patients also have significant risk of developing endometrial and renal cell carcinomas. Since the risk of developing thyroid cancer is not 100%, patients with PTEN mutations following genetic diagnosis benefits from screening thyroid ultrasounds to look for cancer development. Surveillance of patients with PTEN mutations frequently leads to discovery of combination of multiple nodules, goiter, and/or Hashimoto's thyroiditis. Patients can also develop thyroid cancer in PTEN mutation positive cohorts at an early age. Therefore, ultrasound evaluation of thyroids should start as soon as the condition of Cowden syndrome or PTEN hamartoma tumor syndrome is diagnosed in a patient.

Although PTEN mutation was initially thought to be the culprit for the multitude of different variable phenotypic expression, it is now clear that Cowden syndrome is genetically also heterogenous making final recommendations regarding prophylactic surgery especially difficult. Up to 25% of patient meeting Cowden syndrome diagnostic criteria have been found to have negative PTEN mutations. Some patients with Cowden-like syndrome have some features of Cowden syndrome but do not always meet diagnostic criteria or have the germline mutations. These patients can harbor other germline mutations such as succinate dehydrogenase variants (SDHB/C/D), PIK3CA, AKT1, and hypermethylation of KILLIN gene [30]. Hypermethylation of KILLIN, which is a tumor suppressor that affects PTEN, can result in the under expression of PTEN [30].

Treatment of patients with PTEN hamartoma tumor syndrome associated thyroid cancer is frequently a total thyroidectomy. These patients tend to have concomitant thyroid nodules, goiter, and/or thyroiditis in addition to thyroid cancer. In addition, with increased risk of another thyroid cancer in the future, total thyroidectomy seems to be the rational choice for these patients. In terms of prophylactic thyroidectomy, this is an area that is hotly debated, especially after diagnosis of a previous cancer or discovery of benign thyroid nodules or goiters. Prophylactic thyroidectomy needs to be carefully weighed against risks for surgery in patients to minimize morbidity and follow-up mandates. There is a role of prophylactic thyroidectomy in a subset of patients with Cowden syndrome. Since some patients are unable to adequately follow-up for serial ultrasonic examinations of their neck, prophylactic thyroidectomy has been proposed as an option for patients with cognitive deficits who make thyroid ultrasound follow-up difficult to accomplish [32].

5.4 Hereditary Syndrome at Risk for Thyroid Pathology

Familial forms of follicular cell-derived neoplasms constitute approximately 5–15% of non-medullary thyroid cancers [35]. In addition to the genetically and phenotypically heterogeneous Cowden/Cowden-like syndrome, several other familial syndromes can lead to a high rate of thyroid diseases and thyroid neoplasia. Notably, non-medullary thyroid cancers have been found with greater frequency in patients with familial adenomatous polyposis (FAP), Carney's syndrome, DICER1-related syndrome and Werner's syndrome among others. In patients with these syndromes, their thyroid carcinomas tend to be part of heterogeneous diseases, and often has early-onset, multicentricity and bilateral tendencies [35].

Several of the known hereditary cancer syndrome that causes thyroid cancer are autosomal dominant. Both MTC and Cowden syndrome are autosomal dominant hereditary cancer syndrome which leads to an increased risk of thyroid cancer [36–38]. Cowden syndrome is a disease

is both genetically and phenotypically heterogeneous which makes it difficult to determine the exact risk for thyroid cancer. Unfortunately, multiple other genetic conditions that predispose at-risk individuals to thyroid cancer are also heterogeneous in presentation, therefore careful workup of patients with thyroid pathology is a necessity (Table 5.3).

Familial adenomatous polyposis (FAP) is known to lead to increased risk of differentiated thyroid cancer (DTC). The defect caused by the adenomatous polyposis coli (APC) gene carries a risk of up to 12% for development of DTC. In FAP, this autosomal dominant syndrome is caused by germline mutation in the APC gene on chromosome 5q21. Pathognomonic findings are the presence of hundreds of adenomatous colonic polyps that develop early on necessitating total colectomy by the age of 40. Papillary thyroid cancer has a female preponderance and is one of the many extracolonic manifestations of FAP, occurring in 2% of patients. Young women are at particularly higher risk for development of thyroid cancer and their risk is estimated to be 160 times that of normal individuals [35]. These patients frequently have bilateral, multifocal disease and histologically display a rare cribriform pattern. The cells are usually well differentiated and have a spindle pattern, often associated with marked fibrosis. The cribriform-morular variant of PTC, which in contrast to conventional PTC, rarely metastasizes and carries a benign prognosis. Because of the rare occurrence of this type of tumor, its identification raises the possibility of undiagnosed FAP. Patients diagnosed with conventional FAP should also be alerted to the possibility of concurrent thyroid pathology. Intensive screening for thyroid nodules is recommended after the age of 15 years. Prophylactic surgical intervention should also be considered following identification of thyroid nodules. In this patient cohort, it is advisable to perform total thyroidectomy as management of newly discovered thyroid nodules due to the possibility of bilaterally and the high incidence of subsequent thyroid pathology.

Carney's complex is an autosomal dominant disease characterized by skin and mucosal pigmentation [39]. Carney's complex is a condition where there is a gene defect in PRKAR1A gene, leading to the development of blue nevi. Patient with this condition has a relatively lower incidence of DTC, compared to other hereditary cancers, although higher than the general population. These patients often have a variety of endocrine neoplasias as well, including pituitary adenomas, pigmented nodular adrenal disease, and Sertoli and Leydig cell tumors [39]. Patients with Carney's complex usually present with multinodular goiter with adenomatous nodules. Approximately 5–15% of patients with Carney's complex will eventually develop either papillary thyroid cancer (PTC) or follicular thyroid cancer (FTC). Nonetheless, although thyroid cancer risk is increased in these types of patients, the majority are actually afflicted with thyroid goiters leading to the occasional need for thyroid surgeries.

Patients with DICER1 defect are recently undergoing closer scrutiny in terms of their risks for malignancies. These patients most commonly develop pleuropulmonary blastomas which are characterized by tumors that grow in lung tissue or the pleura [6]. Other malignancies seen with DICER1 syndrome include cystic nephromas, Sertoli-Leydig cell tumors of the ovaries, and thyroid cancer. The patients with DICER1 syndrome are known to be at risk of multinodular goiter with occasional development of DTCs. However, recent investigations into DICER1 mutations have uncovered a group of early-onset poorly differentiated thyroid cancers in adolescents and young adults that are pathologically aggressive. This may lead to changes in terms of management options in patients with DICER1 syndrome [6].

Patients with Werner's syndrome develop a curious phenotype of premature aging. Patients with this syndrome are also at increased risk of a variety of neoplasia including benign thyroid nodules and DTCs. Patients with Werner's syndrome have close to 18% risk of developing thyroid cancers with the majority being PTCs [3, 19]. A smaller percentage does develop FTC or the aggressive anaplastic thyroid cancer. Although incidence of DTCs is elevated with Werner's syndrome, the risk is still low that only

Table 5.3 Predisposition syndromes for differentiated thyroid cancer

Hereditary syndrome	Gene defect (chromosomal location)	Pathognomonic feature	Other major diagnostic features	Minor features	Type of thyroid neoplasia	Incidence of thyroid neoplasia
APC-associated polyposis (familial adenomatous polyposis, attenuated FAP, Gardner syndrome, Turcot syndrome)	APC (5q21-q22)	Colonic adenomatous polyps		Extracolonic polyps, congenital hypertrophy of retinal pigment epithelium, soft-tissue tumors, desmoids, osteomas	PTC (cribriform-morular variant) FV-PTC (follicular variant PTC) PTC	0.4–12%
Carney complex	PRKAR1A (17q24.2) "CNC2" (2q16)	Multiple pigmented skin lesions (e.g., nevi, blue nevi, lentigines)	Pigmented nodular adrenals, cardiac myxomas	Thyroid multinodular goiter, melanotic schwannomas, adrenal or pituitary adenomas, hepatocellular carcinoma, pancreatic cancer	PTC FTC	<5%
DICER1 syndrome	DICER1 (14q32.13)	Pleuropulmonary blastoma	Ovarian sex cord-stromal tumors, cystic nephroma, thyroid multinodular goiter	Wilms tumor, rhabdomyosarcoma, ciliary body medulloepithelioma, pineoblastoma, pituitary blastoma, nasal chondromesenchymal hamartoma	FTC FV-PTC PDTC	–
PTEN hamartoma tumor syndrome (Cowden, Bannayan-Riley-Ruvalcaba, PTEN-related proteus, proteus-like syndromes)	PTEN (10q23.2)	Mucocutaneous lesions, cerebellar tumors (Lhermitte-Duclos disease) Breast, endometrial, thyroid cancer, macrocephaly	Breast, endometrial, thyroid cancer, macrocephaly	Fibrocystic breast disease, gastrointestinal hamartomas, lipomas, fibromas, renal cell carcinomas, uterine fibromas	PTC FV-PTC	35%
Werner syndrome	WRN (8q12)	Premature aging, scleroderma-like skin changes	Heart disease, cataracts, short stature, decreased fertility, type 2 diabetes	Melanoma, soft tissue sarcomas, liver cancers, myelodysplastic syndrome	PTC FTC	18%

PTC papillary thyroid cancer, *FTC* follicular thyroid cancer, *PDTC* poorly differentiated thyroid cancer, *FV-PTC* follicular variant of papillary thyroid cancer

enhanced surveillance is recommended without the need for prophylactic thyroidectomy.

Management decisions in patients with thyroid nodules or goiter are influenced by their predisposing hereditary conditions. Even with small tumors (<1 cm), risk of multifocal disease and subsequent neoplasia would favor more aggressive surgical intervention. Therefore, total thyroidectomy often needs to be considered for treatment for small tumors that are incidentally discovered [3, 19].

Patients with Beckwith–Wiedemann syndrome, the familial paraganglioma syndromes, Li-Fraumeni syndromes, McCune-Albright syndrome, and Peutz-Jeghers syndrome are all examples of hereditary syndromes with increased incidence of thyroid cancer [19, 35, 40]. However, the tumors that develop in these patients may not be a direct result of gene defect leading to thyroid neoplasia but rather a global phenomenon due to impaired DNA repair leading to higher incidences of neoplasms. As such, these patients are not routinely considered for prophylactic thyroid surgery or even enhanced mode of surveillance for their thyroid pathologies [40].

5.5 Risk of Prophylactic Thyroidectomy

Surgeon attitude towards prophylactic thyroidectomy has changed significantly with regard to management of hereditary MTC. With genetic sequencing and the risk of malignancy carried by each mutation, timing of surgery can predate the onset of neoplasia. However, surgery on early-onset MTC can also lead to significant morbidities including permanent hypoparathyroidism and recurrent laryngeal nerve injury. Using the National Inpatient Sample hospital discharge data, patients younger than 17 years old undergoing thyroidectomy/parathyroidectomy showed significantly higher risks compared to their adult counterparts [41, 42]. Complication rates for patients separated into age groups (0–6 years, 7–12 years, and 13–17 years) showed an inverse relationship of complications with age groups. Children that are in the 0–6 age group had complication rates as high as 22% compared to 11% for age group of 13–17 [41, 42]. Based on retrospective single-center data, surgical risks are significant in very young patients who are at risk for hereditary MTC [22, 42]. Risk of transient hypocalcemia is as high as 27% and permanent hypocalcemia can be as high as 20% in patients younger than 5 years old [22, 42]. Therefore, risk of surgery needs to be explained and carefully balanced with the risk of development of MTC.

5.6 Conclusions

Surgeon attitude and patient understanding towards management of organ-specific disease entities have changed dramatically over the years. With decreases in surgical morbidity and a clearer understanding that certain genetic conditions predispose patients to malignancies or long significant morbidities, primary organ resection with replacement hormone therapy became an appealing long-term solution over short-term interval surveillance. Due to the availability of genetic screenings for potentially fatal MTC, prophylactic thyroidectomy is one of the few procedures where patients can expect near certainty on the effectiveness of their surgery in reducing risk of cancer. Increasingly, other heritable conditions that lead to increased risk of thyroid malignancy are also being elucidated on their malignancy potential. The role of prophylactic thyroidectomy in these conditions may expand as the accuracy in predicting subsequent malignancy improves, and the risk of surgery becomes less than that of malignancy. Furthermore, the surgical approach in small incidentally discovered tumors would entail total thyroidectomy to prevent subsequent malignancies [3].

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Prophylactic Parathyroidectomy

6

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6.1 Introduction

Four parathyroid glands are present in most individuals, but supernumerary, or a fifth parathyroid has been reported in 6–13% of cases and may arise from division of one or more of the four parathyroid glands during development [1]. The parathyroid glands are located in the anterior neck, posterior to or within the thyroid gland, although may be found from the angle of jaw to the arch of aorta, and weigh 35–40 mg each. They have an important role in the biochemical milieu of the body and dysfunction of hyperparathyroids (hyper or hypoparathyroidism) is associated with serious metabolic consequences that may lead to major morbidity and mortality. Both superior and inferior parathyroid glands, with their blood supply from the inferior thyroid artery, are quite vulnerable to injury during thyroidectomy.

The principal function of the parathyroid glands is regulation of calcium metabolism and homeostasis by direct effects on the kidney, bone, and gastrointestinal tract through PTH actions. While detailed description of the biology and metabolic activities of parathyroid hormone and its relationship with calcium and phosphorus hemostasis is beyond the scope of this chapter, it is important to mention that no study or treatment of parathyroid gland dysfunction can be effective without thorough understanding of anatomy, biology, recent advances in early diagnosis, localization of the pathology, intraoperative localization, and postoperative management of these complex patients. Most recent surgical textbooks provide comprehensive reviews of the subject.

Parathyroidism is the third most common endocrine disorder, after diabetes and thyroid disease. It can be primary, secondary, and tertiary. Primary hyperparathyroidism (PHPT) is caused mainly by three major conditions: parathyroid adenoma (80–90%), parathyroid hyperplasia hormone (PTH) (10–15%), and multiple endocrine neoplasia (MEN1 and MEN2). Finally, on very rare occasions (<1%), parathyroid carcinoma is a cause of primary HPT. Two disorders that must be distinguished from PHPT are familial hypocalciuric hypercalcemia (FHH) and hypercalcemia of malignancy. Both can be diagnosed with simple but careful analysis of biochemical tests.

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The first condition is associated with an abnormal biochemical profile.

Secondary hyperparathyroidism is caused by multiple contributing factors including possible genetic mutation, altered vitamin D metabolism and resistance, impaired calcium response to PTH, retention of phosphorus, and altered metabolism of PTH [2]. The parathyroid glands are intrinsically normal in secondary hyperparathyroidism; however, progressive derangements due to abnormal calcium homeostasis ensue.

Tertiary hyperparathyroidism, on the other hand**,** is rare and occurs in only two conditions: in patients with secondary hyperparathyroidism when parathyroid glands become autonomous and hypercalcemia ensues; the second setting is in transplant patients that do not become eucalcemic because parathyroid glands become autonomous. This occurs in 8.5–53% of transplant recipients, 1% of who will require parathyroidectomy.

Historically, at least two patients have entered the annals of parathyroid surgery as most spectacular failures of parathyroidectomy. Charles Martell, the first parathyroid patient operated on at the Massachusetts General Hospital for severe primary hyperparathyroidism, underwent neck exploration seven times before his parathyroid was found in the mediastinum [3]. Albert Jahne, operated on by Felix Mandl, died of osteitis fibrosa cystica, from four-gland hyperplasia that was not cured with parathyroidectomy [4]. Both Albert Jahne and Charles Martell had persistent or recurrent disease and died of the devastations of uncontrolled hyperparathyroidism. Both cases provided enormous contributions to elucidating the function of the parathyroid glands.

6.2 Conditions to Consider for Prophylactic Parathyroidectomy

Parathyroidectomy is a relatively rare operation. For example, high-volume surgeons are considered those surgeons with >50 cases per year, and in most countries these operations are performed by endocrine surgeons. Surgeons performing 1–15 cases per year are considered lower volume surgeons. Experienced higher volume surgeons have lower rates of persistent or recurrent PHPT [5–7].

Despite significant diagnostic and surgical advances in parathyroidectomy, the optimal timing for surgical treatment in patients with asymptomatic primary HPT is not well established, and controversy exists between high-volume and low-volume surgeons. Obviously, those with high-volume believe that patients should be operated early, prior to disease manifestation associated with primary HPT, while those with lower volume do not. Although physicians may be cautious recommending surgery for asymptomatic patients, NIH has developed criteria for surgery for asymptomatic patients [8]. Surgery thus rests on the premise of future health benefits as well as cure rates that are highest when performed by high-volume surgeons.

6.3 Osteitis Fibrosa Cystica (OFC)

Osteitis fibrosa cystica is a skeletal disorder characterized by loss of bone mass that occurs secondary to PHPT. Elevated levels of PTH cause increased osteoclast activity and consequent bone resorption. This leads to softening of the bones and fractures. Lytic lesions may also develop due to the many multinucleated osteoclast cells. Overt skeletal involvement is extremely rare in most developed countries with prophylactic removal of the parathyroid glands.

OFC can be reversible with removal of the parathyroid gland(s) that contain the adenoma with the goal of preventing advanced skeletal changes. One study of 51 patients with PHPT and skeletal disease or OFC proved a near disappearance of bone pain and regaining of muscular strength in 36 (70.6%) patients by just 1 week following parathyroidectomy [9]. Additionally, all patients with fractures (n = 33) experienced complete healing of the fractures by a median time of 3 months postoperatively after parathyroidectomy. Symptomatic hypocalcemia was evident in 46 (90.2%) patients soon after surgery; however, studies have demonstrated low rates of permanent hypocalcemia [9, 10].

OFC often causes development of brown tumors at multiple skeletal sites, such as the clavicle, ribs, tibia, femur, pelvic bones, and the maxillofacial skeleton. In a study of 22 patients with PHPT and lesions in the maxillofacial skeleton, all underwent parathyroidectomy. All cases demonstrated spontaneous regression of the maxillofacial brown tumors. The vast majority of this regression occurred between months 4 and 20 postoperatively, but regression can occur as early as 1 month and as late as 25 months postoperatively [10].

6.4 Familial Multiple Endocrine Neoplasia (MEN) Syndrome

While the majority of cases of primary hyperparathyroidism are sporadic, 5–10% are inherited as part of a familial syndrome: multiple endocrine neoplasia (MEN), hyperparathyroidism-jaw tumor syndrome, familial hypocalciuric hypercalcemia, neonatal severe hyperparathyroidism, autosomal dominant moderate hyperparathyroidism, or familial isolated hyperparathyroidism.

The management of hyperparathyroidism (HPT) in the setting of familial HPT differs by the specific syndromes and is generally complex because the underlying disease predisposes to persistent and recurrent HPT. The basic principles of parathyroidectomy include achieving and maintaining normocalcemia, avoiding iatrogenic hypocalcemia, and facilitating future surgery for recurrent disease.

Multiple endocrine neoplasia type 1 (MEN1), also known as **Wermer's syndrome**, is a disorder characterized by a mutation in chromosome 11, band 13 of the long (q) arm. The mutation is inherited in an autosomal dominant manner and affects the tumor suppressor gene, *MEN1*, which encodes a 610-amino acid protein, menin. Phenotypically, MEN1 is characterized by the occurrence of parathyroid, pancreatic islet, and anterior pituitary tumors. Hyperparathyroidism is the most common endocrine manifestation in patients with MEN1 [11].

Index cases with MEN1, as well as first-degree relatives, should be offered *MEN1* germline mutation testing. The latter includes relatives who are asymptomatic or who have clinical manifestations of MEN1. Testing of asymptomatic relatives is offered as early as possible, as MEN1 may manifest by 5 years of age. Individuals with *MEN1* germline mutation should be screened on an annual basis thereafter for development of MEN1-associated tumors [12].

Optimal timing and type of surgery for patients with MEN1-PHPT are not well established. Indications for parathyroidectomy include symptomatic or marked hypercalcemia, nephrolithiasis, and evidence of bone disease [12]. Subtotal parathyroidectomy with removal of 3–3.5 glands or total parathyroidectomy with immediate heterotopic autotransplantation of parathyroid tissue is considered and preferable for prophylaxis against end-organ sequelae in kidney and bone. Persistent PHPT, permanent hypoparathyroidism, and recurrent PHPT may occur post parathyroidectomy. Persistent PHPT is more common after subtotal parathyroidectomy than after total parathyroidectomy. However, transitory and permanent hypoparathyroidism is more frequent after total than subtotal parathyroidectomy. The rate of recurrent PHPT is similar for total and subtotal parathyroidectomy [13]. In MEN1-PHPT, all four parathyroid glands are typically adenomatous [12–14]. Removal of less than 3.5 glands leads to unacceptably high rates of recurrent disease in anywhere from 38% to 81% of patients [8]. Parathyroidectomy restores normal serum PTH and calcium levels, but also controls gastrin oversecretion in MEN1 patients with a concomitant active gastrinoma, found in Zollinger–Ellison syndrome (ZES) [13]. ZES is the most common functional pancreatic neuroendocrine syndrome associated with MEN1 and is characterized by gastrin-secreting tumors. Gastrin increases stomach acid production and occurrence of peptic ulcer disease. Hypercalcemia due to HPT in MEN1 worsens hypergastrinemia, thereby exacerbating symptoms of ZES. Thus, the potential benefits of prophylactic parathyroidectomy are considered with MEN1 patients who have severe, medically refractory peptic ulcer disease or other symptoms due to gastrinoma. The surgical procedure of choice for patients with HPT-MEN1-ZES

is excision of precisely 3.5 parathyroid glands [11, 12]. Removal of less than 3.5 glands has an unacceptably high incidence of persistent HPT (42%), while four-gland resection and autotransplant has a high rate of permanent hypoparathyroidism (22%) [11].

Whether or not parathyroidectomy is truly prophylactic for gastrinoma sequelae in MEN1-HPT-ZES is controversial. While some reports show that parathyroidectomy can significantly decrease the fasting gastrin levels, basal acid output, and secretin-stimulated gastrin response [15–20], other studies report little to no effect on these measures of gastrinoma function after parathyroidectomy [21, 22]. However, in a prospective study on 84 patients with ZES-MEN1-HPT who were followed for an average of 17 years, a significant ameliorating effect of parathyroidectomy on gastrin and acid levels was found. The mean decrease in fasting serum gastrin was obtained in 70% of those who underwent parathyroidectomy. Additionally, 20% of patients did not have any biochemical evidence of ZES following parathyroidectomy [4].

Multiple endocrine neoplasia type 2A (MEN2A), also known as **Sipple's syndrome**, is due to various *RET* germline mutations. The presence of a germline mutation at codon 364 predicts high risk of the development of HPT in a MEN2A family [23].

In 1968, Steiner and colleagues described a family with the concurrence of medullary thyroid carcinoma, pheochromocytoma, hyperparathyroidism, and Cushing's syndrome. They suggested that the entity be named multiple endocrine neoplasia type 2 (MEN2). Compared to HTP in MEN1, the hyperparathyroidism experienced by patients with MEN2A is often milder and asymptomatic and may only occur in 20–30% of patients [24].

Genetic testing for *RET* germline mutations should be offered to first-degree relatives of those with hereditary medullary thyroid carcinoma, cutaneous lichen amyloidosis, parents with infants or young children with the classic phenotype of MEN2B, those with Hirschsprung disease and exon 10 *RET* germline mutations, and adults with MEN2A and exon 10 mutations who have symptoms suggestive of HD [25].

While it is well established that total thyroidectomy is necessary for medullary thyroid carcinoma in MEN2A, there is still controversy regarding management of the parathyroid glands. The current standard of care is to leave normal appearing parathyroid glands in situ during thyroid surgery for MEN2A, though prophylactic parathyroidectomy with autotransplantation to the forearm has been supported by some. Yoshida et al. suggest that because the majority of MEN2A patients have normal functioning of the parathyroid glands at time of surgery for medullary thyroid carcinoma, prophylactic parathyroidectomy is indicated in those with MEN2A who have mutation-based high-risk profiles, such as a C634W RET mutation, of HPT in the future [23].

In a cohort of 12 patients diagnosed with MEN2A, total parathyroidectomy with autotransplantation was performed at the time of primary surgery for medullary thyroid cancer. Only 2 of 12 patients showed hyperparathyroidism preoperatively, while the other 10 patients had normal parathyroid function. All parathyroid glands were removed and autotransplanted. Bilateral central neck dissection for medullary thyroid cancer may be difficult if the parathyroid glands are left in situ with sufficient blood supply, as some nodes are closely associated with the parathyroid glands and their blood vessels. During this procedure, attempts to leave the parathyroid glands in place result in either failure to remove all central nodes or devascularization of the parathyroid glands [23].

Of note, prophylactic parathyroidectomy may not be suggested for children and infants with MEN2A. In a study of 50 children with MEN2A, all patients underwent parathyroidectomy with autotransplantation and central neck dissection. However, as hypoparathyroidism is difficult to manage in children, the decision to perform a prophylactic parathyroidectomy should involve an ethical committee [23, 26].

6.5 Familial Hyperparathyroidism

Parathyroid surgery in familial HPT syndromes in the setting of underlying mutations in the calcium receptor (CASR) gene involves radical subtotal parathyroidectomy [24]. Neonatal severe hyperparathyroidism (NSHPT) is a rare and potentially lethal condition caused by germline homozygous inactivating mutations of the *CASR* gene [27]. The *CASR* gene encodes the calcium-sensing receptor (CaSR), which is expressed in the parathyroid and kidney. Inactivating mutations of this gene causes reduced sensitivity of the CaSR to calcium, increased secretion of PTH by the parathyroid glands, and decreased calcium excretion by the kidneys. NSHPT presents in the first few days of life with severe life-threatening hypercalcemia [28]. NSHPT can be fatal if total parathyroidectomy is not carried out within the first weeks of life [27]. As parathyroidectomy surgery can be difficult in the newborn, bisphosphonates and hydration delay parathyroidectomy [29]. During resection, it is imperative to identify all parathyroid tissue, including supernumerary and ectopic glands, as any remnant will become hyperplastic [28].

MEN2A, familial isolated HPT, and HPT-associated with the hyperparathyroidism-jaw tumor (HPT-JT) syndrome typically can be treated with parathyroidectomy, usually subtotal or less. The increased risk of parathyroid cancer in HPT-JT requires special attention.

6.6 Hyperparathyroidism-Jaw Tumor (HPT-JT) Syndrome

Rare conditions, that may lend to prophylactic parathyroidectomy unrelated to the need to correct mineral derangement, are those with germline mutations with high likelihood of development of parathyroid carcinoma. Hyperparathyroidism-jaw tumor (HPT-JT) syndrome is caused by inactivating germline mutations in *CDC73*. Hyperparathyroidism-jaw tumor syndrome has an autosomal dominant pattern of inheritance and is characterized by recurrent parathyroid adenomas, parathyroid carcinoma, Wilms tumor, and fibro-osseous tumors of the mandible and/or maxilla [30]. Similar to MEN1, hyperparathyroidism is the most common feature, occurring in 80% of cases with a mean onset of 32 years of age. Jaw tumors are found in around one-third of cases [24].

In patients with hyperparathyroidism-jaw tumor (HPT-JT) syndrome, the development of parathyroid carcinoma is estimated to be 10–20% [31]. Prophylactic total parathyroidectomy is preferable, in order to lower the risk of parathyroid carcinoma.

Although prophylactic total parathyroidectomy has been previously suggested to reduce the risk of parathyroid carcinoma, selective parathyroid excisions and targeted approaches have recently been proposed as treatment options for HPT-JT as many cases present with uniglandular involvement [27, 30].

6.7 Incidental Parathyroidectomy

Incidental removal of a parathyroid gland during thyroid resection is not uncommon and has been reported in 9–18% of cases [32, 33]. The vast majority of patients (around 85%) experience removal of only one gland. Incidental parathyroidectomy more commonly occurs in patients undergoing a bilateral thyroid resection compared to those undergoing a unilateral lobectomy [32]. A substantial percentage of the cases occur due to the intrathyroidal location of the parathyroid glands; therefore, incidental parathyroidectomy may not be avoidable in these instances [33]. However, one may consider this unintentional prophylactic parathyroidectomy as it occurs with necessary thyroid removal.

6.8 Persistent and Recurrent Hyperparathyroidism

Over 95% of cases with primary HPT will be cured at initial parathyroidectomy; however, persistent or recurrent PHPT occurs in 2.5–5% of cases [34, 35]. Persistent hyperparathyroidism is defined as biochemical evidence of hyperparathyroidism demonstrated within 6 months after parathyroidectomy. Conversely, recurrent hyperparathyroidism is defined as biochemical evidence of hyperparathyroidism demonstrated 6–12 months after parathyroidectomy [36]. Persistent or recurrent disease can occur from remnant parathyroid tissue following subtotal parathyroidectomy, inadequate neck exploration, inexperienced surgeon, inexperience of pathologist, multiple gland disease or from ectopic tissue in the mediastinum or neck, or from a previously placed forearm graft [4, 24]. Other diagnostic dilemmas stem from mild renal disease, sarcoidosis, vitamin D excess, pseudohypoparathyroidism, and malignancy. Diagnostic error is much less frequent with advances in biochemical profiles. Recurrent or persistent hyperparathyroidism is the most resounding, impressive failure of initial operation for hyperparathyroidism. Once a diagnosis of persistent or recurrent hyperparathyroidism is made, surgery is first-line treatment in most circumstances [4].

Though controversy exists regarding indications for reoperative treatment, parathyroidectomy currently remains the only curative treatment option [35]. In circumstances warranting further surgical intervention, >85% of patients have persistent, rather than recurrent disease. One-third of failures are attributed to diagnostic errors although advancements in biochemical analyses have lessened these rates, one-third to ectopic location of the gland, and one-third to inadequate resection of multiple glandular disease. In the majority of cases, when hypercalcemia fails to resolve, it is more likely due to disease persistence, rather than recurrence of the problem.

Reoperation for persistent or recurrent disease, even in asymptomatic hypercalcemia, is about 20% [37] and must be planned carefully. Cervical scarring from previous neck exploration makes the operation more difficult. Structures that must be preserved, such as superior and recurrent laryngeal nerves, are at higher risk of injury due to being obscured from cicatrix. Identifying the target gland itself is more difficult also, due to changes in color. One interesting outcome of recurrent or persistent disease is the fact that a great number of these patients may normalize their calcium for a period of time without surgery. Neither mechanism nor reason for this normalization of biochemical profile is known, so a period of observation may be a good strategy. If beyond 6 months postoperatively there is no normalization, then targeted surgery should be planned and executed. For this, patients should undergo rigorous preoperative diagnostic testing with Tc-99 sestamibi, followed by US-guided FNA for confirmation of parathyroid tissue.

If these two tests are not diagnostic for localization, then selective venous catheterization and sampling of PTH is indicated. This technique is indicated particularly, when a third neck exploration is needed, although second exploration generally has a high likelihood of success. Surgical planning requires unequivocal thorough review of previous operative records and findings. At time of operation, systematic and careful but generous exploration of the neck is a must for any surgeon when operating for persistent or recurrent parathyroidism.

6.9 End-Organ Resistance to PTH

Pseudohypoparathyroidism (PHP) encompasses a heterogeneous group of disorders characterized by end-organ resistance to PTH, resulting in increased serum PTH levels, hypocalcemia, and hyperphosphatemia. Pseudohypoparathyroidism should be distinguished from hypoparathyroidism, in which the parathyroid glands do not secrete enough PTH. PHP is rare, and the prevalence is not well understood [38].

PHP type 1A is characterized by a mutation in the *GNAS* gene, which is inherited in an autosomal dominant manner. The most evident abnormality in these patients is renal PTH resistance;

however, resistance to other hormones such as thyroid stimulating hormone and growth hormone releasing hormone occurs [39].

Diagnosis of PHP type 1A must be made in the setting of normal vitamin D and magnesium levels. Parathyroidectomy for pseudohypoparathyroidism is generally not recommended, as elevated levels of PTH are treated with calcitriol. PTH, calcium, and phosphate homeostasis is monitored via serum levels [38].

6.10 Hypercalcemia Not Cured by Prophylactic Parathyroidectomy

Familial benign hypercalcemia or FHH is an autosomal dominant genetic disorder. Although characterized by hypercalcemia, hypocalciuria, hypomagnesemia, and normal or low parathyroid levels, patients are usually asymptomatic. Further, parathyroidectomy will not produce eucalcemia. Thus, prophylactic parathyroidectomy would not be indicated for this condition of FHH.

Hypercalcemia of malignancy must be differentiated from primary hyperparathyroidism. Direct destruction of bone or cancer stimulated osteoclast activating factors will directly stimulate osteolysis. There are several major mechanisms that account for malignancy-related hypercalcemia, including the excessive tumor production of PTH-related peptide, osteolytic metastatic disease, overproduction of Vitamin D, and parathyroid carcinoma. Pharmacologic therapy is recommended for the management of hypercalcemia of malignancy.

6.11 Surgical Technique and Operative Options

The history of parathyroid surgery developed slowly from case reports, incidental findings, contributions from patients, and scientific studies. Two main surgical approaches have evolved, four-gland exploration versus directed parathyroidectomy. Bilateral cervical exploration of all four glands under general anesthesia is historically the standard of care for definitive treatment of primary hyperparathyroidism. This is usually due to the inability of preoperative imaging to consistently localize the diseased gland and low and inadequate sensitivity in demonstrating multigland parathyroid disease [40]. All four parathyroid glands are identified and assessed intraoperatively, to determine whether multigland disease versus a single adenoma exists. In cases of four-gland hyperplasia, it is necessary for the surgeon to removal all abnormal parathyroid tissue while leaving enough remnant to maintain normal serum calcium levels. Resection of 3 or 3.5 glands or total parathyroidectomy with autotransplantation is performed. Four-gland exploration can be performed through a small cosmetically appearing central neck incision.

In comparison, directed parathyroidectomy is a focused, imaged-guided technique that targets the presumed hyperfunctioning parathyroid gland (adenoma) without need to identify additional parathyroid glands. Minimally invasive approaches use an open technique or a variety of endoscopic approaches. Minimally invasive parathyroid surgery has been adopted at high-volume centers where parathyroid surgery is routinely performed. The image-identified enlarged parathyroid gland is identified and removed.

Endoscopic techniques may enhance visualization although they may not necessarily be a less invasive procedure. A few approaches from the neck can be performed, via lateral cervical or central cervical approach. Central access is better served in bilateral explorations. Bilateral cervical exploration is the ideal operation for most patients with multigland disease, including those with genetic disease.

A variety of minimally access has been created more recently via the axilla, breast, chest, retroauricular space, and floor of the mouth. Endoscopic approaches require experienced endocrine surgeons and careful patient selection and should be avoided in those with prior neck surgery, suspicion of carcinoma, or larger adenomas.

An intraoperative rapid PTH analysis will aid in determining whether additional hyperfunctioning PTH-secreting glands are present and

accompanies minimally invasive if not all techniques. Intraoperative decrease in parathormone level, generally by 50% of preoperative levels on parathyroid excision, predicts operative success and ensures return to normal calcium levels postoperatively.

The biggest challenge of parathyroid surgery is identification of the precise location of the parathyroid glands, and that responsibility lies, for the most part, with the surgeon's expertise.

6.12 Postoperative Complications

Bilateral neck exploration (BNE) seems to have similar outcomes to minimally invasive parathyroidectomy; however, bilateral neck exploration may be accompanied by higher rates of postoperative hypocalcemia. In a meta-analysis on 88 studies assessing outcomes of BNE versus MIP, hypocalcemia occurred in 13.6% of patients who underwent bilateral neck exploration and in 2.3% of patients who underwent a minimally invasive approach. Other complications such as bleeding, infection, and laryngeal nerve injury occurred <1% of the time for both surgical techniques [41]. Injury to the recurrent laryngeal nerve may result in poor voice quality and an increased risk of aspiration. However, if identified intraoperatively, immediate repair may improve voice quality [41–43].

A more severe form of postoperative hypocalcemia following parathyroidectomy is hungry bone syndrome. Hungry bone syndrome is defined as decreased serum total calcium concentration <2.1 mmol/L and/or prolonged hypocalcemia for more than 4 days following parathyroid surgery. Hungry bone syndrome more commonly occurs in patients who underwent surgery for secondary rather than primary hyperparathyroidism. Patients diagnosed with hungry bone syndrome may be treated with high doses of calcium and calcitriol supplementation [44].

Persistent hypercalcemia after parathyroidectomy ranges from 3 to 10% and is usually due to the surgeon's failure to identify and remove all hyperfunctioning glands. Parathyroid surgery performed by experienced endocrine surgeons has a mortality rate near 0% in most series.

6.13 Summary

Parathyroidectomy is a common, first-line treatment option for patients diagnosed with a range of diseases that involve hyperparathyroidism. Prophylactic removal of the parathyroid glands is reserved for a small subset of conditions described above. Benefit is obtained in prophylactic parathyroidectomy for those diagnosed with diseases that are accompanied by an increased risk of developing hyperparathyroidism and related metabolic disturbances and cancer of parathyroid glands. There is true prophylactic benefit in patients diagnosed with multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 2A (MEN2A), neonatal severe hyperparathyroidism (NSHPT), and hyperparathyroidism-jaw tumor (HPT-JT) syndrome, as there is great potential to avoid the hardships associated with hyperparathyroidism and risk of cancer. Nonetheless, the outcomes of all parathyroid thyroid surgery are best in the hands of experienced and dedicated surgeons in parathyroidectomy.

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7 Genetic Predispositions and Prophylactic Mastectomy in Breast Cancer Patients

Atilla Soran and Kazim Senol

7.1 Introduction

World Health Organization (WHO) has considered that the global cancer burden in 2020 is increasing with an estimation of 18.9 million of new cases and 10.1 million deaths from cancer. The International Agency for Research on Cancer (IARC) highlights the incidence, prevalence, and survival rates of 36 types of cancer to identify the etiology and discrepancies between different regions of the world in GLOBOCAN 2018 data [1]. One in 6 women worldwide will develop cancer during their lifetime, while one in 11 dies from the disease. Breast cancer is the most commonly diagnosed cancer among women in 154 of the 185 countries, with 2.1 million new cases each year, contributing to 11.6% of the total global cancer burden [2]. Breast cancer is a leading cause of death among women and ranks for 15% of deaths worldwide [3]. Approximately 522,513 and 276,480 cases of invasive cancer and 140,209 and 42,170 of cancer-related deaths are expected in 2020 in Europe and the United States of America (USA), respectively [4]. In the USA, breast cancer incidence rates have slightly increased by 0.3% per year, compared to the stable death rates in patients aged <50 years since 2007. A decrease in death rates is more evident for older women, and a 1.3% decline per year is observed from 2013 to 2017 [5].

Although there is an increase in the incidence of breast cancer over the years, mortality rates decrease due to the improvements in early diagnosis and treatment modalities. Well-described and significant risk factors are responsible for the development of invasive disease in almost half of the breast cancer cases. Demographic characteristics, familial and reproductive history, environmental and genetic factors have all been described for the development of the invasive disease. Twenty to twenty-five percent of all breast cancer patients present with first- or second-degree family history suggesting genetic cancer susceptibility, as solely 5–10% of genetic predispositions have an autosomal dominant inheritance [6, 7]. The majority of the inherited breast and/or ovarian cancers are associated with a pathologic mutation in breast cancer susceptibility gene-1 (BRCA1) and breast cancer susceptibility gene-2 (BRCA2) [8, 9]. A cumulative breast cancer risk to 80 years old for BRCA1 and BRCA2 carriers is 72% (95% CI 65–79%) and 69% (95% CI 61–77%), respectively [10, 11]. The individuals are also at a higher risk of developing ovarian cancer, with a 44% (95% CI 36–53%) risk for BRCA1 and 17% (95% CI 11–25%) for BRCA2 carriers [12]. BRCA1 and

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BRCA2 mutations are not only a risk factor for breast and/or ovarian cancer in women but also increase the risk of contralateral breast cancer [13], breast and prostate cancer in men [14], pancreas cancer [15], melanoma [16], stomach [17, 18] and serous uterine carcinoma [19], especially in patients with a positive family history with varying rates depending on the individuals' current age and other risk factors. Recent reports have demonstrated that BRCA1 and BRCA2 gene mutations are responsible for hereditary breast cancer in almost 20% of the patients; however, developments in the gene-sequencing technology highlight the relationship between breast and/or ovarian cancer and other hereditary syndromes via determining high-penetrance genes: tumor protein 53 (TP53) mutation in Li-Fraumeni syndrome [20], serine/threonine kinase 11 gene (STK11, also called LKB1) mutation in Peutz-Jeghers syndrome [21], phosphatase and tensin homolog tumor suppressor gene (PTEN) mutation in Cowden syndrome [22], cadherin 1 gene (CDH1) mutation in hereditary diffuse gastric cancer (HDGC) syndrome [23], mismatch repair (MMR) genes (MSH2, MLH1, MSH6, and PMS2) and epithelial cell adhesion molecule gene (EPCAM) mutation in Lynch syndrome [24], partner and localizer of BRCA2 (PALB2) gene mutation [25]. Clinical manifestation of a known mutation in phenotype differs according to the penetrance of the gene. High-penetrance genes are considered for a 40–80% lifetime risk of breast cancer. However, moderate-penetrance genes, including checkpoint kinase 2 (CHEK2), ataxia-telangiectasia mutated (ATM), BRCA1-associated RING domain 1 (BARD1), and RAD51 paralog D (RAD51D), confer a 20–45% lifetime risk of breast and/or ovarian cancer [26].

Genome-Wide Association Studies (GWAS) play a pivotal role in identifying the quantitative traits and common genetic variants in breast cancer susceptibility genes and associated diseases. The primary purpose of these studies is to determine genetic alterations and their linkage with clinical disorders by using DNA microarrays in large-case control populations. Low-penetrance genes are remarkably demonstrated through these gene mapping studies, although there is limited knowledge about their clinical significance through breast cancer inheritance [26]. Recent advances in genetic testing introduced new sequencing techniques. As compared to the conventional Sanger method, Next-Generation Sequencing (NGS) allows sequencing multiple DNA fragments parallelly and rapidly with reduced costs. NGS sequences exponentially higher amounts of DNA samples and gives a precise and sensitive measurement of gene expression levels. High- and moderate-penetrance genes are included in multigene panel testing regarding breast cancer inheritance. In contrast, patients carrying high risk for breast cancer with negative mutations in multigene testing should consider whole genome-wide or exome-wide sequencing in assessing hereditary cancer risk on large panels [27].

As pathological and/or likely pathological variants and variants of the unknown significance of breast cancer susceptibility genes are introduced into the clinical practice in extreme manners, researchers are more prone to elucidate the genetic and epigenetic changes in hereditary diseases caused by genetic inheritance. Therefore, clinicians and researchers worldwide have targeted these mutations to prevent, diagnose, and treat breast cancer and to improve the quality of life of patients and survivors.

7.2 Current Trends in Genetic Testing and Guideline Recommendations

National Institute of Health (NIH) has reported United States of America cancer control measures and current trends in genetic testing in Cancer Trends Progress Report. Genetic testing rates in females aged 18 years and older with a family history of breast and/or ovarian cancer have decreased from 25 to 18% between 2005 and 2010. However, an average increase of 4.4% per year is observed since 2010 in terms of possibility of getting a genetic testing for cancer risk reaching the rate of 22.9% in 2015 [28]. In recent

years, younger women with breast cancer have a pervasive tendency towards genetic testing. Thus, the prevalence of the mutation carriers has been revealed to screen possible risk factors and to provide early diagnosis and treatment. American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), and European Society for Medical Oncology (ESMO) guidelines provide invaluable information for identifying possible candidates and eligibility criteria for genetic testing [29–31].

NCCN guidelines recommend genetic testing for individuals at risk in a broad spectrum including: breast cancer aged ≤45 up to 50 years; triple-negative molecular-type aged ≤60 years; Ashkenazi Jewish at any age; two or primary breast cancer history; ovarian epithelial or fallopian tube cancer, or primary peritoneal cancer; breast cancer at any age with first-, second-, third-degree relative diagnosed breast cancer ≤50 years; male breast cancer; exocrine pancreas cancer at any age; high-grade with Gleason score >7 or metastatic prostate cancer. Guidelines have also expanded the suggestions for genetic testing in patients who are at risk for hereditary breast and/or ovarian cancer (HBOC). Patients with a close blood relative to whom genetic testing was interpreted as a pathologic/likely pathogenic variant in a susceptibility gene are referred for cascade testing to demonstrate germline status of high- and moderate-penetrance gene mutations for the patient and family members. Centers for Disease Control and Prevention have considered cascade testing as a tier 1 genomic application for patients with Lynch syndrome and HBOC [23, 32]. Previously limited testing for patients meeting the criteria above resulted in 6–10% of misdiagnosis in mutation rates of BRCA1 and BRCA2 genes, especially before 2006. Multigene testing is highly recommended for previously tested individuals to determine potential mutations in other breast cancer susceptibility genes. In addition to these recommendations mentioned above, The American Society of Breast Surgeons has suggested that genetic testing has to be applicable for individuals with a personal history of breast cancer [33].

7.3 Hereditary Breast Cancer Surveillance and Risk-Reducing Treatments

7.3.1 Surveillance

Identification of a pathological and/or likely pathological mutation in a specific allele and genetic inheritance renders possible surveillance and early management of the risk-reducing therapeutic options for patients with or without breast cancer. Surveillance should be prioritized depending on patients' age, personal and familial history of breast and other cancer, the first onset of cancer in a family member, and expectations of childbearing [30]. BRCA mutation carriers must consider breast awareness and self-examination starting at age 18, regular expert clinical breast examination every 6–12 months starting at age 25, and contrast-enhanced magnetic resonance imaging (MRI) annually starting at age 25–29 followed by annual mammography (MG). Adjunctive utilization of MG and MRI increases the detection rates of breast cancer in the early stages up to 94% and decrease mortality rates at 5 years [34]. A recent meta-analysis, which stratified patients by mutation status and age, has demonstrated the contribution of MG to MRI resulted in a 3.9 and 12.6% increase in screening sensitivity of BRCA1 and BRCA2 mutation carriers, respectively. Besides, adjunctive MG also contributes to screening sensitivity in BRCA2 mutation carriers under 40 years old, indicating that distinct and personal screening scheme has to be taken into consideration according to the mutation status [35].

7.3.2 Chemoprevention

Risk-reducing surgeries and chemoprevention are substantial therapeutic options for high-risk patients carrying a 40–50% lifetime risk of cancer. There are limited data in the literature regarding the preventive benefit of hormonal chemoprevention in BRCA1 and BRCA2 mutation carriers. National Surgical Adjuvant Breast and

Bowel (NSABP) Breast Cancer Prevention Trial (P-1 trial) has revealed a 62% risk reduction (relative risk [RR] 0.38, 95% CI 0.06–1.56) in breast cancer with tamoxifen in BRCA2 mutation carriers, similar to the reduced incidence of estrogen receptor-positive breast cancer among all women [36]. In contrast, tamoxifen did not improve breast cancer incidence among healthy BRCA1 mutation carriers aged 35 and older in the P-1 trial (RR 1.67, 95% CI 0.32–10.07). BRCA1 mutation carriers have a tumor more likely to be high-grade medullary morphology with basal-like immunophenotype, which lacks estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2, and increased tp53, cytokeratin 5/6, cytokeratin 14/17, and epidermal growth factor [37]. Hormonal chemoprevention is less effective as a risk-reducing option for BRCA1 mutation carriers seeking surveillance without mastectomy. Recent studies proposed decreased rates in ipsilateral recurrence and contralateral breast cancer with adjuvant tamoxifen therapy in BRCA mutation carriers. Preventive benefits of aromatase inhibitors in mutation carriers are lacking in the literature; however, extensive chemoprevention studies provided decreased breast cancer risk in high-risk postmenopausal patients with aromatase inhibitor therapy [38, 39].

7.4 Hereditary Breast Cancer and Risk-Reducing Surgery

7.4.1 Bilateral Prophylactic Mastectomy

Risk-reducing surgery in high-risk patients and BRCA mutation carriers yields remarkable success in preventing the development of primary breast cancer, ipsilateral breast cancer recurrence, contralateral breast cancer, and ovarian cancer. Prophylactic mastectomy (PM) and prophylactic salpingo-oophorectomy (PSO) are the mainstays of the therapeutic procedures with favorable outcomes regarding genetic inheritance. High- and moderate-penetrance genes in mutation carriers present with a 5- to 20-fold increase in breast and subsequent cancers, although it has been shown that PM reduces the risk of ipsilateral and contralateral breast cancer by 90–97% especially in patients with BRCA1 and BRCA2 mutations (Table 7.1) [68].

In 1998, Hartmann et al. have conducted a retrospective analysis of 639 women who underwent bilateral PM with the diagnosis of high- and moderate-risk of breast cancer depending on the family history. This study has presented a significant risk reduction in breast cancer incidence and breast cancer-related deaths in bilateral PM patients compared to the predicted deaths according to the risk-assessment models and incidence of breast cancer in close relatives at a median follow-up time of 15 years [47]. The latter study, including a retrospective analysis of BRCA mutation carriers in the same cohort of patients, revealed that bilateral PM was provided complete risk reduction in 26 mutation carriers with no evidence of breast cancer after a median of 13.4 years of follow-up [48]. Meijers-Heijboer et al. have demonstrated in a prospective study that bilateral PM in BRCA mutation carriers was consistent with 100% risk reduction in invasive disease during 3 years follow-up, whereas surveillance had a 2.5% risk of breast cancer per year [49]. However, this study had a bias in favor of risk-reducing surgery regarding premenopausal PSO rates, which were 58% and 38% in bilateral PM and surveillance groups, respectively. Prevention and Observation of Surgical Endpoints (PROSE) study group has prospectively matched the bilateral PM and surveillance group of patients based on PSO and has confirmed a relative breast cancer risk reduction of 95% in patients with prior or concurrent PSO and 90% in patients with intact ovaries [50]. Domcheck et al. have presented 2482 women who tested positive for BRCA1 and BRCA2 mutation with similar breast cancer risk reduction in both bilateral PM and PSO group. However, breast cancer incidence was significantly reduced among BRCA1 patients who had a PSO before 50 years old (HR = 1.36; 95% CI: 0.26–7.05, $p = 0.02$). PSO and bilateral PM have also significantly reduced the breast cancer incidence in BRCA1 and BRCA2 mutation carriers without previous breast cancer, but PSO did not affect ipsilateral

Table 7.1 Hereditary syndromes and clinical significance of associated genes in familial breast cancer, and guideline recommendations for risk-reducing and screening options for mutation carriers

	Genes and associated syndrome	Associated tumors	Lifetime risk of breast cancer (%)	Breast cancer risk and incidence, median age, and tumor subtype	Breast cancer management and surveillance	
					NCCN recommendations [29]	ESMO recommendations [30]
High-penetrance genes	BRCA1, hereditary breast and ovarian Cancer [11, 39, 40]	Gynecologic, pancreatic and prostate tumors, melanoma	60% by age 70 (95% CI 44–75%)	Incidence 1/300 Relative risk 11.4 Median age 42 years Triple negative, basal-like tumors	Breast awareness at age 18 Clinical breast examination every 6–12 months starting at age 20–25 years or individualized based on breast cancer history in a relative before 30 years Annual mammography with consideration of tomosynthesis, annual contrast-enhanced MRI starting at age 30–75 years Recommend risk-reducing salpingo-oophorectomy between 35 and 40 years Consider risk-reducing mastectomy	Clinical breast examination every 6–12 months starting at age 25 years, or 10 years before the first onset of cancer in a relative, annual contrast-enhanced MRI starting at age 25 with the addition of mammography starting at age 30 Recommend risk-reducing salpingo-oophorectomy at age 35–40, consider risk-reducing mastectomy
	BRCA2, hereditary breast and ovarian Cancer [11, 39, 40]		55% by age 70 (95% CI 41–70%)	Incidence 1/800 Relative risk 11.7 Median age 45 years Luminal phenotype tumors		
	TP53, Li-Fraumeni syndrome [41, 42]	Soft tissue sarcomas, brain and adrenocortical tumors, medulloblastoma, leukemia No increased risk of ovarian cancer	85% by age 60 (95% CI 60–92%) [31]	Incidence 1/5000 to 1/20,000 Relative risk 6.4 (95% CI 4.3–9.3) Median age 33 years (range 22–60) Increased HER-2 receptor-positive tumors	Clinical breast examination every 6–12 months starting at age 20 years, annual contrast-enhanced MRI at age 20–29 years Annual contrast-enhanced breast MRI or mammography at age 30–75 years Consider risk-reducing mastectomy Avoid therapeutic radiation therapy	Clinical breast examination every 6–12 months starting at age 20–25 years, annual contrast-enhanced MRI starting at age 20–75 or if MRI is unavailable, mammography may be considered starting at age 30 Consider risk-reducing mastectomy Avoid radiation therapy
	CDH-1, hereditary diffuse gastric Cancer syndrome [22, 43]	Gastric tumors No increased risk of ovarian cancer	39% by age 80 (95% CI 23–68%) [22]	Incidence unknown Relative risk 6.6 (95% CI 2.2–19.9) Median age 53 years Invasive lobular carcinoma	Clinical breast examination every 6–12 months starting at age 20–25 years Annual mammography with consideration of tomosynthesis, annual contrast-enhanced MRI starting at age 30 years Consider risk-reducing mastectomy	Clinical breast examination every 6–12 months starting at age 20–25 years, annual contrast-enhanced MRI starting age at 20–29, annual MRI and/or mammography starting at age 30–75 years Consider risk-reducing mastectomy

(continued)

Table 7.1 (continued)

Genes and associated syndrome	Associated tumors	Lifetime risk of breast cancer (%)	Breast cancer risk and incidence, median age, and tumor subtype	Breast cancer management and surveillance	
				NCCN recommendations [29]	ESMO recommendations [30]
PTEN, Cowden syndrome [44, 45]	Endometrial, thyroid, gastrointestinal and renal tumors No increased risk of ovarian cancer	77% by age 70 (95% CI 59–91%)	Incidence 1/200,000 Relative risk is unreliable Median age 42 years [34–38, 46–49] Increased risk of benign breast changes	Clinical breast examination every 6–12 months starting at age 20 years Annual mammography with consideration of tomosynthesis, annual contrast-enhanced MRI starting at age 30–35 years, or 5–10 years before first onset of breast cancer in a relative, endometrial cancer screening starting at age 35 Consider risk-reducing mastectomy and hysterectomy	Clinical breast examination every 6–12 months starting at age 20–25 years, annual contrast-enhanced MRI starting and/or mammography starting at age 30–75, annual endometrial ultrasound ± biopsies at age 30–35 Consider risk-reducing mastectomy and hysterectomy
STK11, Peutz-Jeghers syndrome [50, 51]	Mucocutaneous pigmentation, hamartomatous polyps, gastrointestinal system cancers, pancreas, ovarian, and other gynecologic cancers, gonadal tumors	45% by age 70 (95% CI 27–68%)	Incidence 1/155,000 Relative risk 15.2 (95% CI 7.6–27) (1,113,065) Median age 37 years (range 9–44) Invasive ductal carcinoma	Clinical breast examination every 6–12 months starting at age 20 years, Annual contrast-enhanced MRI at age 20–29 years, annual breast MRI or mammography at age 30–75 years Risk-reducing mastectomy is not recommended and may be considered based on family history	Clinical breast examination every 6–12 months starting at age 20–25 years, annual contrast-enhanced MRI starting at age 20–29 years, annual breast MRI and/or mammography starting at age 30–75 years Consider risk-reducing mastectomy
PALB2, familial breast Cancer [24, 52, 53]	Pancreas	35% by age 70 (95% CI 26–46%)	Incidence 1/100 to 4/100 Relative risk 5.3 (95% CI 3–9.4)	Clinical breast examination every 6–12 months starting at age 20 years Annual mammography with consideration of tomosynthesis, annual contrast-enhanced MRI starting at age 30 years Consider risk-reducing mastectomy	Clinical breast examination every 6–12 months starting at age 20–25 years, annual contrast-enhanced MRI starting age at 20–29, annual MRI and/or mammography starting at age 30–75 years Consider risk-reducing mastectomy

	MSH1, MLH1, MSH6, PMS2, EPCAM, lynch syndrome [54, 55]	Colon, endometrium, ovarian, and stomach	18.6% by age 70 (95% CI 11.3–26%)	1/370 to 1/3000 Median age 53 years Relative risk 3.95 (95% CI 1.59–8.13)	Clinical breast examination every 6–12 months starting at age 20 years Annual mammography beginning at 40 years of age with consideration of annual contrast-enhanced breast MRI, Consider risk-reducing hysterectomy and salpingo-oophorectomy after completion of childbearing Consider risk-reducing mastectomy depending on the family history	Annual endometrial ultrasound ± biopsies at age 30–35 Consider risk-reducing hysterectomy and salpingo-oophorectomy after completion of childbearing
Moderate-penetrance genes	CHEK2, familial breast Cancer, c.100delC [56–58]	Male breast cancer, stomach, colon, prostate, kidney and thyroid tumors, sarcoma No increased risk of ovarian cancer	28–37% by age 70 (95% CI 20–56%)	Relative risk 3.0 (95% CI 2.6–3.5) Mean age 50 years Luminal phenotype tumors	Clinical breast examination every 6–12 months starting at age 20 years Annual mammography beginning at 40 years of age with consideration of annual contrast-enhanced breast MRI Consider risk-reducing mastectomy depending on the family history	Clinical breast examination every 6–12 months starting at age 20–25 years, annual contrast-enhanced MRI starting age at 20–29, annual MRI and/or mammography starting at age 30–75 years
	ATM, Familial Breast Cancer [59]	Ovarian, pancreatic, and prostate tumors	32.8% by age 80 (95% CI 24.5–40.3%)	Incidence 1/40,000 to 1/300,000 Relative risk 2.8 (95% CI 2.2–3.7) Median age 40–50 years	Clinical breast examination every 6–12 months starting at age 20 years Annual mammography beginning at 40 years of age with consideration of annual contrast-enhanced breast MRI Consider risk-reducing mastectomy depending on the family history Consider risk-reducing salpingo-oophorectomy depending on the family history	Consider annual breast MRI (no evidence regarding the age of onset)

(continued)

Table 7.1 (continued)

Genes and associated syndrome	Associated tumors	Lifetime risk of breast cancer (%)	Breast cancer risk and incidence, median age, and tumor subtype	Breast cancer management and surveillance	
				NCCN recommendations [29]	ESMO recommendations [30]
RAD51 paralog D, Familial Breast Cancer [60] RAD51 paralog C, Familial Breast Cancer [60]	Ovarian cancer, lung, kidney, brain, pancreatic, liver, colorectal tumors	9% by age 80 for ovarian cancer	Incidence <1/1000 Relative risk for ovarian cancer is 6.3 (95% CI 2.8–13.8) Median age for ovarian cancer is 60 years No evidence of association for breast cancer Relative risk for breast cancer 0.91 (95% CI 0.45–1.86) Triple-negative breast cancer	Unknown or insufficient data for breast cancer risk, recommend breast cancer screening based on the family history Consider risk-reducing salpingo-oophorectomy at age 45–50 or depending on the family history	Consider risk-reducing salpingo-oophorectomy after the age of 45
BRIP1, Familial Breast Cancer [61]	Ovarian cancer, Fanconi anemia	5.8% by age 80 for ovarian cancer (95% CI 3.6–9.1%)	Incidence 1/100 Relative risk for ovarian cancer is 11.2 (95% CI 3.2–34.1) Median age for ovarian cancer is 50–55 years Triple-negative breast cancer	No evidence of association for breast cancer risk, recommend breast cancer screening based on the family history Consider risk-reducing salpingo-oophorectomy at age 45–50 or depending on the family history	Consider risk-reducing salpingo-oophorectomy after the age of 45
NBN, familial breast Cancer, c.657del5 [62, 63]	Prostate cancer	20–30% by age 80	Incidence 1/167 Relative risk 3.1 (95% CI 1.4–6.6)	Annual mammography beginning at 40 years of age with consideration of annual contrast-enhanced breast MRI Risk-reducing mastectomy and salpingo-oophorectomy is not recommended and may be considered based on family history	N/A
BARD1, Familial Breast Cancer [64]	Neuroblastoma, lung and colon cancer	20% by age 80	Incidence <1/1000 Relative risk 2.16 (95% CI 1.31–3.63) Triple-negative and bilateral breast cancer [65]	There are no specific management and surveillance guideline for breast cancer risk in mutation carriers Surveillance should be individualized	N/A

	NF1, Neurofibromatosis Syndrome [66]	Malignant peripheral nerve sheath tumors, GIST No increased risk of ovarian cancer	20% by age 80	Incidence 1/3000 to 1/5000 Relative risk 2.6 (95% CI 2.1–3.2) Median age 46 years Invasive ductal carcinoma Breast cancer risk decreases over 50 years	Annual mammography beginning at 30 years of age with consideration of annual contrast-enhanced breast MRI at age 30–50	N/A
Low-penetrance genes	MUTHY RAD50 MRE11A FANCC RECQL4 RINT1 SLX4 SMARCA4 XRCC2 [52]		<20% lifetime risk of breast cancer in mutation carriers.	Up to 1.25-fold increase for heterozygous mutations Up to 1.65-fold increase for homozygous mutations	There are no specific management and surveillance guideline for breast cancer risk in mutation carriers Surveillance should be individualized	N/A

breast recurrence in mutation carriers [69]. Risk-reducing surgeries not only reduce breast and ovarian cancer incidence but also improve survival rates among females in both BRCA1 and BRCA2 mutation carriers [70]. To date, the survival benefit of bilateral PM was controversial. An exploratory study conducted by Ingham et al. mentioned 10-year survival rates of BRCA1 and BRCA2 mutation carriers without prior breast cancer following risk-reduction surgery as 98.9% (92.2–99.5%) and 98% (91.1–99%), respectively. This study has improved survival for bilateral PM and PSO procedures by linking first-degree relatives to the BRCA mutation carriers to overcome the bias of tapered interests in genetic testing on diagnosis [71]. Thus, survival benefit regarding PM requires further prospective studies in a large cohort of patients with long-term follow-up. BRCA mutation carriers have the highest risk for breast and ovarian cancer, whether they have an intense surveillance program and options for risk-reducing surgery. Several studies have investigated the survival benefit or survival gain from bilateral PM via theoretical modeling in BRCA mutation carriers [72, 73]. The estimated gain in life expectancy was declined by aging and was minimized for patients older than 60 years. Recent modeling proposed 25.6% of patients will die of the disease without risk-reducing surgery before 80 years old, which could be avoided by mastectomy at age 25. BRCA mutation carriers would gain 2.6 and 3.3 years of life expectancy from bilateral PM at age 35 and age 25, respectively [74].

7.4.2 Contralateral Prophylactic Mastectomy

The tendency of genetic testing is tremendously increasing in young women with breast cancer, and clinical management is relatively confusing for patients seeking for surveillance and surgical treatment [75, 76]. Breast-conserving surgery and radiotherapy result in favorable outcomes and survival rates in sporadic breast cancer so that the role of local therapy for mutation carriers is debated with conflicting clinical outcomes in the literature [77]. Ipsilateral breast cancer recurrence and contralateral breast cancer following breast-conserving surgery and radiotherapy are significantly increased in mutation carriers as compared to the sporadic cases [78, 79]. Ipsilateral breast cancer recurrence risk in a patient who has an evident family history is increasing up to 13% at 10 years after the diagnosis of primary disease [80]. BRCA mutation carriers have a contralateral breast cancer risk of 17% at 5 years and 30% at 10 years or almost 3% per year after breast-conserving surgery [81, 82]. Prophylactic contralateral mastectomy (CM) should be considered for high-risk patients to minimize these risk factors and tumor recurrences. Younger age at disease onset, history of PSO, and unilateral mastectomy have been presented as predictors of contralateral prophylactic mastectomy in women with a BRCA1 or BRCA2 mutation [83]. Sprundel et al. have demonstrated in a retrospective study, including 148 BRCA mutation carriers who treated for invasive breast cancer stages I–IIIa, that prophylactic CM reduced the risk of contralateral breast cancer 91% regardless of PSO [84]. The survival benefit of prophylactic CM was found to be related to the PSO in that cohort of patients. Metcalfe et al. have reviewed the 20-year survival experience of 390 BRCA mutation carriers with early-stage breast cancer and suggested that patients treated with bilateral mastectomy have an increased likelihood of survival than those treated with unilateral mastectomy [85]. The survival rates of bilateral and unilateral mastectomy groups were 88% and 66%, respectively, with a significant 48% reduction in death from cancer for prophylactic CM (HR:0.52 95% CI 0.29–0.93, $p = 0.03$). These studies have identified the breast cancer risk reduction and survival benefit of prophylactic CM, but the data were insufficient to distinguish the preventive effects of PSO from the CM on survival. Evans et al. have compared the survival rates of prophylactic CM and non-CM in patients with BRCA mutation and matched the groups by mutation type, PSO, tumor grade, and stage [86]. This study has demonstrated significantly better survival rates for prophylactic CM,

regardless of PSO. Thus, more extensive series would indicate prophylactic CM as a counseling option on diagnosis to improve survival.

7.4.3 Operative Approaches

Prophylactic mastectomy procedures include total mastectomy, skin-sparing mastectomy, and subcutaneous (nipple-sparing) mastectomy. In a prospective study, local recurrence rates of skin-sparing mastectomy were found to be 0–7% comparable to the total mastectomy [87]. A meta-analysis of nine retrospective series comprising 3739 patients has also demonstrated similar local recurrence rates in between skin-sparing and total mastectomy procedures [88]. There has been no randomized controlled trial comparing the efficacy and oncologic safety of the nipple-sparing mastectomy with total mastectomy and skin-sparing mastectomy. Local recurrence rates, 5-year disease-specific survival rates, and mortality rates were similar for nipple-sparing and skin-sparing mastectomy procedures in several studies [89]. Nipple-sparing mastectomy is controversial in BRCA mutation carriers due to the remaining substantial amount of breast tissue, which provides a higher risk for breast cancer recurrences during postoperative surveillance [50]. However, Jakub et al. have retrospectively reviewed the outcomes of nine institutions' data from 1968 to 2013 in a cohort of patients with BRCA mutations in terms of oncologic safety of prophylactic nipple-sparing mastectomy. They have presented no ipsilateral or contralateral breast cancer recurrence in any patients who underwent nipple-sparing mastectomy within a median follow-up time of 36 months [90]. Although follow-up times after risk-reducing surgery were insufficient to make precise comments, such studies have also demonstrated the efficacy and the oncologic safety of nipple-sparing mastectomy in BRCA mutation carriers [91, 92]. While nipple-sparing mastectomy and immediate reconstruction with breast implants is the most preferred procedure, multiple experienced centers have implicated this procedure into routine clinical practice for risk-reducing surgery [93, 94].

7.5 Conclusion

Clinical management is relatively confusing of breast cancer patients with gene test positivity. Since studies are providing more information for breast cancer genes, guidelines for genetic counseling and testing are changing frequently. Therefore, regarding surgery or surveillance in the group of patients should be discussed case by case with their input and discussion from all stakeholders including genetic consular and patient.

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8 Prophylactic Mastectomy for Benign Pathologies

Murat Kemal Atahan and Beyza Özçınar

8.1 Introduction

Two topics should be mentioned under the topic of prophylactic mastectomy for benign pathologies. One is bilateral prophylactic mastectomy (BPM) for high-risk patients with no breast cancer history, the second is contralateral prophylactic mastectomy for patients with single-side breast cancer. We will discuss each topic separately.

Breast cancer is the most common cancer and cause of cancer-related deaths in women all over the world. About one in four cancers in women are breast cancer. GLOBOCAN 2018 data show that around 2.1 million new breast cancer cases are diagnosed in 2018 and about 15% of cancer-related deaths of women are due to breast cancer [1]. It is known that when breast cancer is diagnosed in the early stages, it provides a survival advantage for women and the most important outcome in cancer is survival. Accordingly, the following question arises: would we also gain a survival advantage if we identify high-risk women and perform risk-reducing surgery for breast cancer?

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Breast cancer is a multifactorial disease and about 15–20% of all cases have a family history, but only 5–10% have a known genetic mutation [2–5]. Family history is a well-known risk factor for breast cancer. The risk of breast cancer in women with affected first-degree (parents or siblings) relatives increases about two times, and the occurrence of both increases approximately four times [2–4, 6]. However, it is known that the risk increases as the family member becomes closer and the age of diagnosis decreases [2, 4, 5]. Although the most common genetic mutations are seen in BRCA 1 and 2 genes, only 9–29% of patients who underwent genetic counseling for familial breast cancer have these gene mutations. Approximately 4–11% had other genetic mutations and no known genetic mutation was detected in approximately 64–86.5% of these patients [7].

According to the National Comprehensive Cancer Network (NCCN) 2020 Breast Cancer Risk Reduction Guideline, women with a known genetic predisposition or pedigree suggestive of genetic predisposition or lifetime risk are ≥20% in models, and if the life expectancy is ≥10 years, they should be counseled for risk-reduction options [8]. Also, women who do not meet any familial risk criteria or have negative genetic tests but have a history of thoracic radiation therapy before 30 years, history of lobular carcinoma in situ (LCIS), or history of atypical ductal or lobular hyperplasia (ADH, ALH) or 5-year breast cancer risk of ≥1.7% and life

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expectancy ≥10 years should be counseled for risk-reduction options [8].

The topic of "Genetic Predispositions and Prophylactic Mastectomy" has been discussed in the previous section. In this section, we will discuss: prophylactic mastectomy for high-risk women with no known genetic mutations and contralateral prophylactic mastectomy for patients with unilateral breast cancer.

8.2 Prophylactic Mastectomy for High-Risk Women with No Known Genetic Mutation

8.2.1 Assessment of Breast Cancer Risk

When conducting breast cancer risk analysis, detailed medical, surgical, and family history should be obtained. Especially, whether there was a history of radiation therapy to the thoracic region before age 30 years, benign previous biopsy (especially LCIS, ADH, or ALH) and the number of biopsies, reproductive history (age at menarche, age at menopause, age at first pregnancy, and age at first living birth), use of oral contraception and hormone replacement therapy, number of relatives with breast cancer history on each side, blood degree, age at diagnosis, bilaterality, and ethnicity of women should be considered. Statistical models are used to determine the risk of breast cancer. The Claus model can be used especially for risk analysis of Caucasian women with a family history of one or more relatives with breast cancer. The Claus model is primarily focused on family history. The Gail model can be used for women over 35 years of age, but this model excludes genetic predisposition and second- or third-degree family history, it includes benign previous biopsy. The Gail and Tyrer-Cuzick (IBIS) models use demographic information of patients, i.e., age, personal history of breast disease, reproductive history, and family history. The most commonly used model is the Gail model. However, the Gail model underestimates the risk in non-Caucasian women, women with atypia, and mantle radiation history. The Tyrer-Cuzick model overestimates the risk in LCIS, ADH, and ALH, but can be used in women aged below 35 years. In addition, the BRCAPro and BOADICEA models can be used to calculate the mutational probability [9, 10].

Genetic counseling and genetic testing are recommended according to the National Institute for Health and Care Excellence (NICE) guideline, last updated in November 2019, if any of the below are present:

1. First-degree relative with breast cancer aged under 40 years.
2. Two first-degree relatives or one first- and one second-degree relative with breast cancer at any age.
3. First-degree male relative with breast cancer at any age.
4. First-degree relative with bilateral breast cancer, first diagnosed before age 50 years.
5. First-degree relative with both breast and ovarian cancer.
6. Any first- and/or second-degree relatives one with breast cancer, one with ovarian cancer [11].

In addition to the above NICE criteria, the NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Guideline 2020 recommended that women with a familial history of first- and/or second-degree relative with pancreatic cancer, metastatic or intraductal prostate cancer at any age or more than 5% BRCA 1 and 2 mutation risk in the Tyrer-Cuzick, BRCAPro, and Penn II models should undergo genetic counseling [12]. Prophylactic mastectomy for patients with pathologic mutations was discussed in the previous section. The group of patients without a genetic predisposition but high risk for breast cancer will be discussed in this section.

8.3 Prophylactic Mastectomy for Women with a History of LCIS or ADH/ALH

Lobular carcinoma in situ (LCIS), ALH, and ADH are benign breast lesions with known increased breast cancer risk. LCIS and ALH will

be referred to as lobular neoplasia together in this section. The rate of lobular neoplasia to progress into ductal carcinoma in situ (DCIS) or invasive cancer is 8–10 times higher for LCIS and 4–5 times higher for ALH than the breast cancer risk in the general population [13, 14]. Hartman et al. (2014) in their cohort study of 698 women with ADH and/or ALH, after a mean follow-up of 12.5 years, found that 29% of all women had developed breast cancer at 25 years after biopsy diagnosis. Two in every three patients with breast cancer were diagnosed on the ipsilateral side with atypical hyperplasia, and one in three had cancer on the contralateral side, 19% of all cancers were DCIS, and the remainder was invasive cancer. Moreover, the risk of progress into invasive cancer was similar both in ADH and ALH in this cohort [15]. These results support that atypical hyperplasia, either ADH or ALH, is a risk indicator of breast cancer that increases the risk of both breasts. Coopey et al. (2012) revealed that after a mean follow-up of 68 months, the results of 2938 women with atypical breast lesions showed that the 10-year breast cancer risk was 17.3% in ADH, 20.7% in ALH, and 23.7% in LCIS [16]. In a review, Thomas et al. (2018) concluded that the rate of breast cancer development in 1-year duration was 1–2% for ADH and ALH, and 2% for LCIS [17, 18].

The upgrade rate of atypical lesions to cancer after excision is also important. A large retrospective study by Chang Sen et al. (2016) showed that 447 lesions with ALH or LCIS in biopsy resulted in 22 cancers after excisional biopsy, and the upgrade rates of LCIS and ALH were 8.4% and 2.4%, respectively. The authors recommended close follow-up with 6-month intervals for ALH and surgical excision for LCIS [19]. In many studies, the upgrade rate of ADH into cancer was between 10 and 30%, and most authors recommended surgical excision for ADH [20–22]. Pena et al. (2017) found that the upgrade rate of ADH was 16%. However, when they divided the cases according to the number of atypical foci, the upgrade rate of the low-risk group was found as 4.9%. They concluded that, in the low-risk group of ADH, active surveillance was enough, but in the high-risk group, surgical excision was recommended [23].On the other hand, some studies have suggested that ADH had a lower upgrade rate than previous studies and there was no need for excision, especially in the low-risk group [22, 24]. Menen et al. (2017) followed 175 patients with ADH with low risk for 3 years. They performed surgical excision on 50 patients and close follow-up with 125 patients, and the rate of cancer development in the surgical excision group was 12%, and 5.6% in the follow-up group. Index site failure was detected only in one patient, but a striking point was that all contralateral breast cancers occurred in the surgical excision group. They concluded that observation was appropriate in selected cases of ADH with low risk [22]. In the review of Racz et al. (2017), the authors concluded that excision was recommended for lobular neoplasia, especially for LCIS, and surgical excision was the standard treatment for ADH; however, in some selected low-risk cases of ADH, observation could be applied safely [25].

There are three strategies for the management of high-risk women, and there are no randomized controlled trials for the management strategies of LCIS, ADH, and ALH. Wong et al. (2017) used the Markow simulation model and created three cohorts in the SEER (National Cancer Institute's Surveillance, epidemiology, and End Results) database to determine life expectancy and survival differences in three cohorts (active surveillance, risk-reducing chemoprevention, and bilateral prophylactic mastectomy) in patients with LCIS. The results showed that adding chemoprevention or risk-reducing surgery increased life expectancy. Chemoprevention added an average of 1.6 months and risk-reducing surgery added an average of 3 months to survival. However, in the quality-adjusted life expectancy (QALE), a decrease in survival was detected. Bilateral prophylactic mastectomy (BPM) reduced QALE by about 1.9–3.7 years. BPM reduced the risk of breast cancer by 99%, but only provided a maximum of 4.4 months of gain to women diagnosed at the age of 40 years. As a result, the 10-year overall survival (OS) with active surveillance was 97.4% for women diagnosed at the age of 40 years, and there were 0.3–0.4% increases with chemoprevention and 0.5–0.7% increases with BPM [26].

In light of these data, chemoprevention seems to be the most appropriate approach in LCIS. The contribution of BPM to survival seems to be negligible considering its negative effect on quality of life. A long-term follow-up study of King et al. (2015) of 56 women with LCIS who underwent BPM revealed that no patients had cancer in the follow-up; 1032 women remained under surveillance with or without chemoprevention, and after a mean follow-up of 83 months, 14% of women had breast cancer. Women who preferred BPM were younger with dense breasts and strong family history. Chemoprevention was significantly associated with breast cancer risk reduction [18].

Consequently, in the presence of lobular neoplasia or ADH, to decide whether BPM indicated, the biopsy results alone are not sufficient. It is important to determine the lifelong risk of breast cancer by using the most appropriate risk-determining model according to other risk modifiers such as family history, prior radiation therapy history, and reproductive history. The Gail, Tyrer-Cuzick, and Claus models can be used. Claus model is useful when there is a strong family history, and the Gail model is useful for women aged ≥35 years who have other risk factors, e.g., age at menarche, age at first live birth, and the number of breast biopsies. The Gail model may underestimate the risk of hyperplasia. The Tyrer-Cuzick model can be used before age 35 years, but it overestimates the risk of LCIS, ADH, and ALH. By using these methods if the lifelong risk is ≥20%, BPM is considering as an alternative treatment option. However, the effect of BPM on survival, the advantages and disadvantages of this method, and possible complications should be explained to women in detail and all three treatment options should be presented for choice.

8.4 Prophylactic Mastectomy for Women with a Previous History of Thoracic Radiation Therapy

Many studies have shown that women receiving radiation therapy (RT) to the chest region due to Hodgkin lymphoma (HL) before age ≤30 years have an increased risk of developing breast cancer. The risk of developing breast cancer after childhood radiation therapy to the chest is about the same as that for women who are BRCA-positive [27–29]. Travis et al. (2005) observed 3817 women receiving radiation therapy to the chest due to HL and showed that if a woman at age 25 years received radiation therapy, the risk of developing breast cancer by 45 years was 11.1% and was 20% by 55 years [27].The Late Effects Study Group reported a cohort of 1380 children with HL; after 17 months follow-up, they found an 18.5-fold increased risk in second malignancies, with breast cancer being the most common malignancy with a risk of 56.7 times that of the general population [28]. The International Late Effects of Childhood Cancer Guideline Harmonization Group recommends starting a breast cancer surveillance at age 25 or 8 years after RT (whichever occurs last). Especially for those who receive ≥20 Gy RT to the chest, annual breast cancer surveillance is recommended at least up to age 50 years [29]. The NCCN Breast Cancer Risk Reduction Guideline version 2020 recommended that risk-reduction options should be discussed with women who have a prior history of chest RT before age 30 years with a life expectancy of ≥10 years [8].

8.5 Contralateral Prophylactic Mastectomy

In recent years, the frequency of recommending bilateral mastectomy to women with unilateral cancer has increased. However, bilateral mastectomy has no advantage in many women. There are certain consensus statements about which women are eligible for contralateral prophylactic mastectomy (CPM). Consequently, the advantages and disadvantages of CPM should be evaluated on a patient-by-patient basis, and also the patient's preference should be considered in the decision process. The American Society of Breast Surgeons (ASBrS) consensus group agreed that CPM was not recommended in women with average risk with unilateral breast cancer [30].

Wong et al. (2017) compared patients who underwent breast-conserving surgery (BCS) and a CPM group; after a median follow-up of 8.25 years, they found that the OS and breast cancer-specific survival (BCSS) in the BCS group was better than in the CPM group (HR: 1.08) [31]. BCS should be recommended for every suitable woman.

If a woman needs a mastectomy due to the index tumor then consider the patient's overall survival rate according to the age, prognostic features of index tumor, patient's comorbidities, and risk of contralateral breast cancer (CBC) occurrence rate and systemic recurrence rate. It should be noted that the CPM does not alter the prognosis of the original tumor, so CPM should be considered if it provides a survival advantage.

In their systematic review and meta-analysis, Molina-Montes et al. (2014) revealed that the 5-year cumulative risk of CBC in BRCA 1 and 2 carriers was 15% and 9%, and in noncarriers it was 3% [32]. The risk of CBC in women with average risk was 0.1–0.6% per year [30]. In the WECARE study, the relative risk of CBC in patients with a first-degree relative with a history of breast cancer diagnosed before age 45 years was 2.5 and the relative risk was 3.6 in patients with a family history of first-degree relative with bilateral breast cancer. In women diagnosed with unilateral breast cancer before age 55 years with a first-degree relative with breast cancer, the 10-year CBC risk was 15.6%. The risk of CBC in women with a first-degree relative with bilateral breast cancer was similar to that of genetic mutation carriers [33].

There is no randomized controlled trial showing the survival benefit of CPM. There are many studies in the literature showing the survival advantage of CPM; however, the survival advantage may be due to the selection bias of patients, e.g., those with younger age and no comorbid diseases. Peralta et al. (2000) compared two groups of patients matched in terms of age, tumor stage, surgical modality, and adjuvant therapy, and they found the 15-year disease-free survival (DFS) rate as 55% in the CPM group and 28% in the non-CPM group, and CBC was detected during the 6.2 years' follow-up in 36/182 patients with unilateral mastectomy [34]. In a retrospective cohort study of 50,000 women with unilateral breast cancer, the CBC rate in the CPM group was 0.5% during the 5.7 years of follow-up and 2.7% in the group without CPM, and the HR of death of breast cancer was 0.57 [35].

A study of patients who underwent CPM from the SEER database between 1998 and 2010 showed that patients with increased age, greater tumor size or nodal involvement, poorly differentiated histology, and estrogen receptor (ER) negativity had an increased risk of death due to cancer and CPM had a survival benefit. However, if patients with CBC were excluded from the analysis, the survival advantage of CPM did not change. This condition suggests that patients who underwent CMP may already have a better prognosis and this survival benefit might result from a selection bias of cases [36]. In the systematic review and meta-analysis of Fayanju et al. (2014), patients who underwent CPM had better OS (RR: 1.09) and a reduced risk of breast cancer-related death (RR: 0.69) than those non-CPM patients. In a group of high-risk women due to family history or genetic predisposition, there was an absolute risk reduction of CBC in the CPM group, but there was no survival advantage detected. The researchers commented that the increase in survival in CPM group was not due to a decreased rate of CBC cancer but might be due to selection bias of patients with younger age and better health [37]. As a result, excluding the BRCA carriers, CPM is not associated with survival benefit [30]. The NCCN Breast Cancer Guideline 2020 recommended that CPM should be discouraged for women with unilateral breast cancer other than high-risk women recommended in Breast Cancer Risk Reduction Guideline 2020 [8, 38].

As a result of the consensus statement of the ASBrS, CPM should be considered in women with BRCA1-2 mutation, strong family history without known genetic predisposition, and women with a history of chest radiation before age 30 years. CPM can be considered in women with a strong family history and negative genetic result and carriers of genes other than BRCA 1-2, e.g., CHEK-2, and p53 [32].

8.6 Surgical Outcomes

There are risks and benefits of prophylactic mastectomies. BPM and CPM reduce breast cancer risk by more than 90% [30, 39–42]. Hartmann et al. (1999) studied 639 women with moderate-to-high risk for breast cancer according to their family history, and the 14-year follow-up results concluded that the breast cancer occurrence rate decreased 89.5% in women with moderate risk and 90–94% in women with high risk. Also, breast cancer-related death decreased 100% in women with moderate risk and 81–94% in women with high risk who underwent BPM [39]. Boughey et al. (2010) revealed the results of 385 women with stage 1 and 2 breast cancer who had a family history and showed that CPM reduced the CBC rate about 95% and had better 10-year OS rates (83% vs.74%) and DFS with an HR of 0.67 [40].

Generally, mastectomies have low morbidity and also decrease the anxiety of recurrence. Several studies showed higher surgical complications rates with either BPM or CPM. In the study of Miller et al. (2013), CPM was associated with a higher rate for any surgical complications (OR: 1.53) and also a higher risk for major complications (OR: 2.66) [43]. All women need breast reconstruction after BPM or CPM. In women with implant-based reconstruction, the overall complication rate was 1.2 times higher in the bilateral mastectomy group, and with autologous reconstructions, the rate was 1.6 times higher than in the unilateral mastectomy group. However, surgical site infections, implant failure, and medical complications were similar in both the unilateral mastectomy and bilateral mastectomy groups [44]. BPM and CPM can also increase complications rate requiring reoperation, and potential comorbidities increased these risks. The occurrence of any major complications delayed the adjuvant treatment and indirectly affected the survival outcome.

The cosmetic results of unilateral mastectomy may be worse than bilateral mastectomy and reconstruction, especially in patients with unilateral breast cancer. CPM may be considered for good cosmetic results, to improve breast symmetry and also to reduce the anxiety of CBC. Women with unilateral mastectomy are less satisfied by their body image than those who undergo bilateral mastectomies [42]. On the other hand, women with bilateral mastectomies have decreased sexual satisfaction and feel themselves to be less sexually attractive. Additionally, many patients reported the results to be worse than expected. However, women who choose BPM tend to be more anxious regarding breast cancer occurrence and BPM decreases their anxiety level.

Therefore, the risk–benefit analysis of both BPM and CPM for each patient should be well discussed with the patient whose preference should be considered. Any women at high risk for breast cancer should be considered for BPM, and women at high risk for CBC should be considered for CPM. However, if the primary tumor is advanced and patients have several comorbidities, which would increase the risk of surgical complications and have no increased risk of CBC, CPM should be discouraged [30].

8.7 Conclusion

The prophylactic mastectomy decision is a highly personal decision and wtext fomen should be informed that the risk of breast cancer does not disappear with prophylactic mastectomies, only reduced by 90–95%, and that every surgical modality has potential risks and sometimes reoperations may be required.

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9 Prophylactic Surgery for Liver Pathologies

Osman Nuri Dilek, Feyyaz Güngör, and Arif Atay

9.1 Introduction

The liver is an organ blessed with the fate of the person in Babylon in 2000s before Christ. Glisson has identified the liver capsule with cadaver studies and published it as a book in 1654. With the definition of anesthesia and infection control in the late nineteenth century, abdominal surgical interventions entered the surgical practice. Partial liver resection performed by Lius in a 67-year-old woman with liver adenoma in 1886 was recorded as the first liver surgery [1]. This was followed by resection with Pasquelin's cautery, partial resections made by Bruns (1888), "V"-shaped (wedge) resections made by Keen (1889), and hemangioma resections (1893) by von Eiselberg. Cantlie defined the invisible anatomic border (1897) between the right and left lobes. The maneuver applied by Pringle in 1908 to prevent bleeding in patients with liver trauma has been developed as a method of Pringle maneuver, which is still used today. Wendel performed the first successful right hepatectomy in 1911 due to hepatocellular carcinoma. Tinker successfully resected the first hemangioma rupture case in 1935. During the world wars, shock physiology and liver anatomy and physiology were better understood [1]. These surgeries were followed by hepatectomies by Ishiyama (1941), French Lortat-Jacob et al. (1951), and Japanese Honjo et al. (1949, 1953). Lin (1960) from Taiwan described the finger fracture method for the separation of liver tissue in 1950 and published his series of 34 cases in 1960 with 12.1% mortality and 19% 5-year survival rate [1, 2]. In the 1950s, Hjortsjo and Couinaud described segmental anatomy. Later, Couinaud's work led to the adoption of the segment classification concept, which was also taken under his name. Knowing the segmental anatomy also initiated the processes that could contribute to preserving liver tissue [1, 3].

Following the first liver transplantation in 1963, there has been a great change in liver surgery in the last 50 years. In the 1980s, subsegmental resection concept was developed by Makuuchi et al. (1990) [3]. In a cirrhotic patient, it was also important to remove the tumor, leaving sufficient liver tissue. Indocyanine green (ICG) test developed by Makuuchi et al. played an important role in determining liver functionality. Makuuchi criteria (includes ascites, bilirubin, and ICG-15 min retention rate) became an important criterion for safe resection. The same team later developed the portal vein embolization

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technique, which would enable hypertrophy of the left lobe to prevent remnant liver failure. In the last two decades, liver resections have started to be performed safely with laparoscopic and robotic surgery. Preservation of the liver reserve is one of the most important factors affecting survival and success in liver surgery. New horizons have been opened in front of tissue-preserving resections with three-dimensional imaging and navigation systems.

In this section, the conditions related to prophylactic liver surgery will be discussed under the heading of benign pathologies, malignant pathologies and special conditions of the liver.

9.2 Benign Hepatobiliary Pathologies

9.2.1 Hemangiomas

Hemangiomas are the most common benign liver tumors. The vast majority of hemangiomas are asymptomatic and are detected randomly. The prevalence is reported to be 1–20% in the general population [4–6]. It is 1–6 times more common in women. They show multiple locations in 9–22% of cases. Capillary hemangiomas are usually small, peripherally located, and sometimes multiple. Cavernous-type hemangiomas appear less and can reach larger diameters. Hemangiomas larger than 5 cm in diameter are called giant hemangiomas [4, 6–8]. Although most are asymptomatic, pain and abdominal discomfort are the most common symptoms. Different degrees of thrombosis, calcification, and fibrosis can be observed in large lesions (Fig. 9.1) [6, 9]. Ultrasonography is diagnostic but in suspicious cases, the diagnosis should be confirmed with contrast-enhanced USG (CEUS), CT, and MRI. Contrast-enhanced MRI is the most important determinant in differential diagnosis. Sensitivity and specificity are more than 90% [10].

There is no direct relationship between the size of hemangioma and complications. However, there is a relationship between the characteristics of the lesion and clinical symptoms. The size of the hemangioma may increase during pregnancy

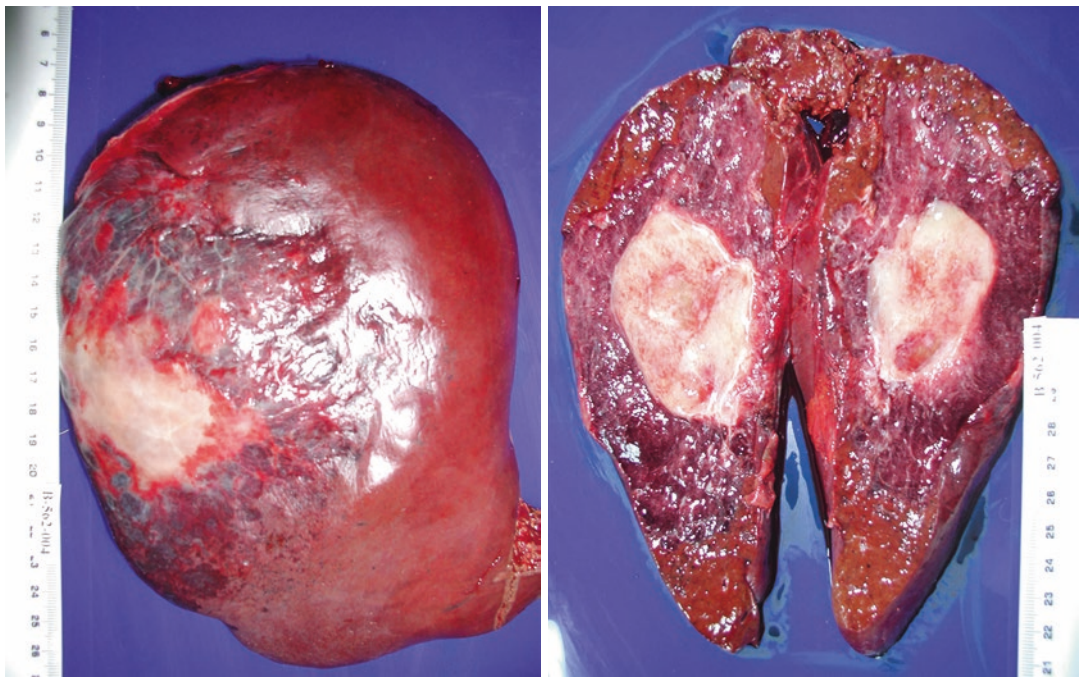

Fig. 9.1 The specimen and cross-sectional surface of our patient undergoing right hepatectomy due to giant hemangioma and thrombocytopenia

or with estrogen therapy. Conter and Longmire (1988) stated that they believe that estrogen therapy contributes to the development and growth of hemangioma. However, the exact mechanism of hormonal effect has not been adequately clarified [7, 8, 11]. This raises the question that prophylactic surgery should be performed in the women population who want to become pregnant and have hemangioma. However, the literature data are limited in this regard. It is reported that estrogen can cause an increase in the size of the lesion, but spontaneous rupture rates are similar for pregnant and nonpregnant women. In the literature, patients who underwent enucleation due to lesion enlargement and pain that reached 10 cm in diameter 1 year after birth were reported [12].

In the follow-up of patients, it should be decided by looking at the size and location of hemangioma with clinical findings and imaging [10]. Asymptomatic patients are monitored and prophylactic surgery is not recommended. Patients' personal findings, location, and features of hemangioma should be evaluated together. It is recommended to evaluate patients with symptomatic (abdominal pain and compression symptoms) and lesion diameter >10 cm by a multidisciplinary team (hepatologist, hepatobiliary surgeon, interventional radiologist, and pathologist) [6, 9]. According to the EASL guide, diagnosis and follow-up with USG is sufficient for 3 cm lesions in healthy individuals. They can use pregnancy or oral contraceptives. In oncology or liver patients, differential diagnosis should be made with CT or MRI. In typical cases, monitoring is sufficient. Patients with clinical or compressive symptoms and developing Kasabach–Merritt syndrome should be evaluated with a multidisciplinary approach [6].

Curry et al. (2020) recommend performing magnetic resonance imaging (MRI) within 6–12 months when the diameter of the lesion is >5 cm. They reported that lesions with a growth rate of ≤3 mm per year were monitored for up to 2 years, if the lesion was growing less than 3 mm per year, and there was no need for further imaging of MRI in 6–12 months, if the lesion appeared stable. If the lesion continues to grow more than 3 mm per year, the patient should be evaluated by a multidisciplinary team for prophylactic surgery [10].

The first complication that comes to mind about hemangiomas was bleeding. There is no clear information about the risk of hemangiomas spontaneous bleeding. In a hundred-year literature review by Donati et al. (2011), they reported that rupture was reported in 97 hemangioma cases, 46 of which were spontaneous and 51 were non-spontaneous [9]. Non-spontaneous ruptures are more common in people under 40 years of age. The bleeding risk of symptomatic hemangiomas is calculated as 1–5%. It is stated that ruptures can be of any diameter (1–37 cm), but hemangiomas with an average diameter of 11 cm and above have a higher risk of bleeding. Mortality risk due to rupture bleeding was calculated as 35–75% [9, 13, 14].

The preferred surgical methods for the treatment of hemangiomas are liver resection or enucleation [15, 16]. There is no consensus on the optimal treatment of large hemangiomas. The rupture of hemangiomas appears to be a very exceptional case, and prophylactic resection is not recommended in asymptomatic cases [5]. Prophylactic surgery can be performed in cases with clinical symptoms, leading to consumption coagulopathy (consumptive coagulopathy-Kasabach-Merritt syndrome), or patients with pressure symptoms or larger than 10 cm in diameter [9]. The procedure to be performed may vary depending on the location and size of the lesion. In appropriate cases, enucleation may be the first method of choice.

Preoperative transarterial embolization can be used to reduce the lesion size in cases where resection may be difficult by location and in patients with a diameter of 10 cm. Arterial embolization may reduce the risk of bleeding in surgery [9, 13, 14, 17, 18]. It has been also reported that hemorrhage in the ruptured hemangioma can be controlled with the same method [19, 20]. Although enucleation has been reported as preserving more hepatic parenchyma and reducing postoperative complications than anatomical liver resections, the appropriate approach to the patient, the surgeon's preference and experience,

and the location of the lesion are also determinative in the form of treatment [15].

9.2.2 Hepatocellular Adenomas

Hepatocellular adenomas are rare, solid, and benign liver lesions. They are seen most commonly in women. The incidence is 1/1,000,000 years old and the risk increases 30–40 times in those using long-term oral contraceptives. Adenomas are usually unique and rarely can be multiple. The use of estrogen-containing oral contraceptive drugs in young women has an important place in the etiology. Lesions regressed after discontinuation of the drug. In addition, patients with glycogen storage disease or metabolic syndrome have a higher risk of developing adenoma [4, 21].

The greatest risk for adenomas is the possibility of rupture. However, the estimation of rupture incidence has been reported from 25 to 64% in the literature, although it is difficult, as it is mostly obtained from data of symptomatic patients. Risk factors for bleeding include large lesion (>5 cm), hormone use, pregnancy, exophytic and subcapsular location, and histopathological subtypes [22, 23].

The transformation risk of adenomas into hepatocellular carcinoma has been reported between 0 and 18% in the literature [21]. The risk of malignancy is higher in male sex (10 times greater), and in patients with lesions greater than 5 cm, height of AFP and activation of beta-catenin histopathologically [21, 22, 24].

Asymptomatic patients can be followed, but despite all precautions, considering spontaneous rupture and malignant transformation in lesions >5 cm in size, patients are candidates for prophylactic surgery and should be evaluated with a multidisciplinary team [25].

9.2.3 Focal Nodular Hyperplasia

Focal nodular hyperplasia (FNH) is a benign liver lesion caused by the proliferation of hyperplastic hepatocytes around a central star-like scar. Focal nodular hyperplasia is the second most common benign solid tumor of the liver, with an estimated prevalence of 2.5–8% [4, 26]. Typically, FNH is more common in women, and female sex hormones are the biggest risk factors for FNH [27, 28].

They are generally asymptomatic since they are located peripherally. The prognosis for FNH is generally excellent because the lesion is mostly stable or may regress over time. Complications such as bleeding and compression are rarely reported, and malignant transformation has not been reported [29–32]. In laparotomies performed for other reasons, peripheral locations can be removed for differential diagnosis. Prophylactic surgery is not recommended in patients with definitive diagnosis.

9.2.4 Cystic Lesions

Cystic lesions of the liver can be simple, tumoral, infectious, hemorrhagic, and traumatic. Differential diagnosis is important for determining the treatment. Simple cysts of the liver are clear fluid-containing cystic formations that are not related to the intrahepatic biliary tract. Although simple cysts are present in about 1% of the population, very few grow and even less cause symptoms [33]. Simple cysts tend to occur more commonly in the right lobe and are more prevalent in women. The female-to-male ratio is approximately 1.5:1 among those with asymptomatic simple cysts, while it is 9:1 in those with symptomatic or complicated simple cysts. Huge cysts are found almost exclusively in women over 50 years of age [34]. Rarely, their size can range from a few millimeters to massive lesions occupying the upper abdomen [35]. It is sufficient to monitor most of the simple diagnosed simple cysts. Simple and large volumes of simple cysts can cause tension, pain, and pressure symptoms (Fig. 9.2). Most simple cysts can be treated with aspiration and sclerotherapy. Prophylactic surgery is rarely required, and the most appropriate option is unroofing. Prophylactic unroofing can be performed to reduce tension and pressure in the presence of common cystic lesions in the liver, kidney, and pancreas [36].

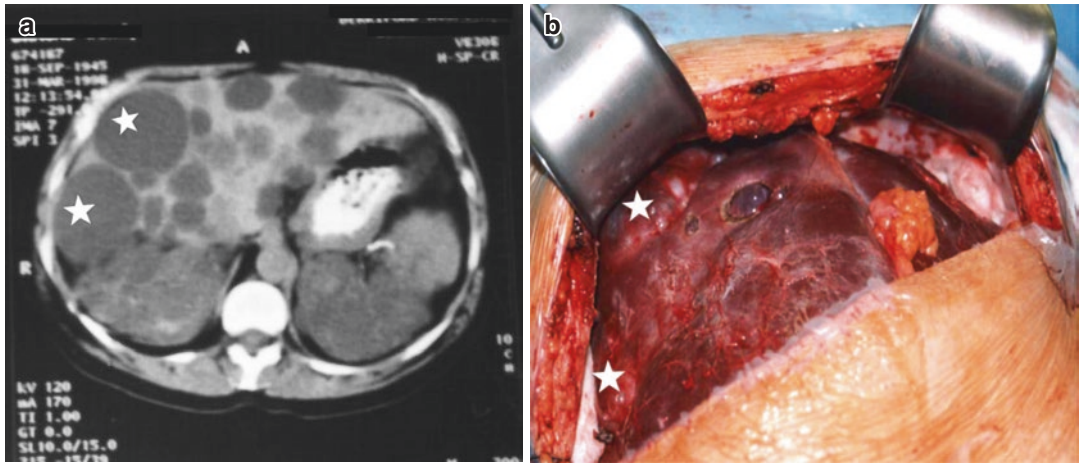

Fig. 9.2 Axillar CT section (**a**) with multiple liver cysts (stars) and the appearance of cysts in our patient who underwent laparotomy for unroofing (**b**)

Cystic lesions with malignant character (cystadenomas) can be confused with benign cysts. Malignant degeneration should be suspected in the presence of wall irregularities, solid components, and septations [33]. Treatment of tumoral cystic lesions is definitive surgery. When mucinous cystic neoplasia or other rare cystic neoplasia is suspected, it should be evaluated with a multidisciplinary team.

9.2.5 Caroli's Disease

Caroli's disease is a congenital anomaly of the biliary tract of the liver, characterized by multifocal saccular dilatations in the biliary tract. Also known as a type 5 biliary tract cyst. It is a disease characterized by cholangitis due to stasis and stones formed in vesicles in the bile duct. It has a hereditary transition feature. It can hold the entire liver or be limited to the sector or lobe. In medical treatment, ursodeoxycholic acid is used. However, antibiotic and supportive therapy and endoscopic interventions may be required in recurrent cholangitis attacks [33]. Due to the chronic inflammatory process of the disease, hypoproteinemia and developmental retardation may occur. Cholangiocarcinoma develops in 7% of patients. Liver transplantation can be performed in diffuse lesions. In cases involving the lobe or sector, lobectomy is sufficient [4].

9.2.6 Biliary Atresia

Biliary atresia is the most common cause of jaundice of the newborn requiring surgical treatment. In patients with biliary atresia, which is usually diagnosed in the months after birth, bile drainage should be performed rapidly in order to prevent liver damage and cirrhotic process (see Chap. 11). Roux-en-Y type hepatoportoenterostomy (HPE) is the standard treatment method in the treatment of biliary atresia. HPE can be applied with laparoscopic and open surgery. However, complications such as fistula and stenosis developing in the early postoperative period are important causes of morbidity and mortality [37]. In clinical studies, it is recommended to perform HPE primarily in patients with biliary atresia, since prophylactic liver transplants to be performed in the early period do not achieve the desired success due to the small size of the baby and technical difficulties. In the follow-up of HPE cases, liver tissue is within normal limits in approximately one-third of the cases after 4 years. Approximately half of the cases require liver transplantation due to stenosis in the biliary tract or liver failure [38]. It is recommended that corrective restoration attempts to be performed in cases with stenosis are not successful, and liver transplantation should be performed instead of corrective procedure due to the growth of children [39].

9.3 Malign Liver Pathologies

9.3.1 Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related deaths worldwide [40]. In cases with HCC, the survival time is shortened due to the rapid progression of the disease or the cirrhosis to decompose. Especially in patients with high risk of recurrence or early recurrence after resection, prophylactic liver transplantation can provide a longer survival. Yang et al. (2016) reported that longer survival can be achieved with prophylactic liver transplantation in selected cases with gene expression, microvascular invasion, poor differentiation, and presence of microsatellite lesions [40, 41].

9.3.2 Simultaneous Lesions

About half of malignant tumors in the liver are metastatic lesions. The most common metastases are colorectal, breast, and bronchial origin. In 10–25% of cases with colorectal cancer, there is liver metastasis when diagnosed [42, 43]. In the follow-up of patients, more than half of the cases (50–75%) develop synchronous or metachronous liver metastasis. The chance of resection can be obtained in 10–40% of patients with metastases undergoing chemotherapy [43–45]. There are different opinions about the timing and treatment of metastatic liver tumors. In the conventional approach, resection of the metastases is recommended. Some of the resections can be synchronized with the colorectal process, as well as before or after the lesion location, number, and size. In the literature, studies report that there is no statistically significant difference between simultaneous and staged resections and it can be performed in appropriate cases [46]. In a multicentric study conducted in Korea, 3-year survival was reported to be better in the two-staged surgery group than in the simultaneous surgery group [47]. In the clinical series of 226 cases of Nanji et al. (2017), they reported that the operation performed in the liver was more limited (number, size, and width of the resection) in the patient group undergoing synchronous resection [48].

Besides neoadjuvant chemotherapy increases the chance of surgery, there are opinions that the damage caused by the liver (steatohepatitis, sinusoidal obstruction syndrome, remnant liver insufficiency, etc.) negatively affects morbidity and mortality [49]. However, there are also studies indicating that it contributes to the reduction of the number and diameter of metastatic lesions with neoadjuvant chemotherapy, increases operability, and does not have a negative effect on morbidity and mortality [50, 51]. In recent years, better results have been achieved with effective chemotherapy protocols. Pathological complete recovery (CPR) is very low (4–11%) in patients undergoing neoadjuvant chemotherapy protocols, but this rate rises to 35–50% in patients who are considered to have complete clinical recovery (CCR) [43]. Gustavsson (2012) reported that he applied oxaliplatin or irinotecan protocols with fluorouracil, recommended in the NCCN guidelines, and did not recommend performing prophylactic resection in patients with colorectal cancer (if there is no perforation, obstruction, and bleeding). He also states that the diameter and number of liver metastases have decreased in patients receiving chemotherapy and their incidence decreased to 10% [42]. However, it should be kept in mind that as a result of the examination of the lesions that are regressed or thought to be lost after chemotherapy, complete resection can be achieved in 20% of the cases, live tumor cells are not completely eliminated, and this may pose a significant risk for relapse, survival, and follow-up [44].

There are different results regarding tumor-free margin in the resection of metastases. While it has been advocated to remove metastases with 1 cm of normal liver tissue in the past years, it is now reported that metastases can be removed with 1 mm tumor-free margin. Besides, it has been reported that metastasectomies performed by separating the metastatic mass from vascular structures adjacent to its anatomical border also have a positive effect on survival [52–54]. There are also studies reporting that there is no difference between new chemotherapy regimens and

R0 and R1 resections [52, 55, 56]. On the other hand, the presence of tumor-specific mutant DNA up to 4 mm in liver tissue around metastasis has been demonstrated [57]. Resections with wider normal liver tissue should be preferred in appropriate cases to reduce the risk of local recurrence and protection.

9.3.3 Incidental Solitary Lesions

Incidental solitary liver lesions are detected more with increasing use of radiological imaging methods. Most of them are asymptomatic and benign, and they are detected incidentally in radiological scans. Definitive diagnoses are usually made and further investigations are rarely needed. In cases where incidental lesions are detected, whether the patient has a history of cirrhosis, hepatitis, and malignancy should be questioned first [58]. Surgical resection is rarely required to diagnose incidental solid liver lesions, but it can be performed for lesions of uncertain etiology, which are symptomatic. If the possibility of HCC cannot be excluded despite the absence of risk factors (cirrhosis, chronic liver disease, etc.), prophylactic surgical resection can be performed for risk-reduction method and histological verification [59]. It is recommended to evaluate the patients by a multidisciplinary team (hepatologist, hepatobiliary surgeon, interventional radiologist, and pathologist).

9.4 Miscellaneous Conditions

9.4.1 Portal Hypertension

Portal hypertension is a pathology that usually develops as a result of cirrhosis, schistosomiasis, or extrahepatic portal vein thrombosis. Portal hypertension is a result of increased resistance to portal blood flow and can lead to complications such as variceal bleeding and ascites. One-third of patients with cirrhosis develop variceal bleeding, which is a major cause of morbidity and mortality [60].

Numerous prophylactic procedures have been described to prevent cirrhosis-related complications [61, 62]. In addition to beta blockers, endoscopic band ligation and sclerotherapy are used in emergency, elective, or prophylactic treatment of esophageal varices (see Chap. 13). AGA guidelines are used today to prevent bleeding of esophageal varices [60]. More than 90% of cases are successful with a medical and endoscopic approach. However, the bleeding recurs in 60–70% of cases within 2 years after the index bleeding [63, 64].

Randomized studies comparing surgical portocaval shunts with medical therapy in cirrhotic patients were conducted in the 1970s. Although surgery is highly effective in preventing variceal bleeding and ascites production, new problems such as high risk of complications and encephalopathy are encountered after surgery [60, 65, 66]. For this reason, it has been determined that prophylactic portocaval shunts do not show the expected benefit, and deaths due to liver failure are higher than esophageal variceal hemorrhages and these techniques have started to be applied in selected cases. Apart from the shunts, there are other options (non-shunt) such as terminal esophagoproximal gastrectomies, esophageal transections, and Sugiura procedure to prevent esophageal variceal bleeding. These procedures can be performed for therapeutic purposes as well as for prophylactic purposes [67].

In patients with non-cirrhotic portal hypertension, it has been shown to be the opposite of the situation, and deaths due to esophageal variceal bleeding are higher [68]. Pal et al. (2005) showed that prophylactic distal splenorenal shunts to be performed in patients with non-cirrhotic portal fibrosis are successful in preventing bleeding, and the symptoms of splenomegaly, ascit, and hypersplenism regressed in most patients [68].

Transjugular intrahepatic portosystemic stent shunting (TIPS) is another method used in bleeding prophylaxis in patients with portal hypertension [69]. Sinusoidal and portal decompression can be achieved with TIPS without the risk of general anesthesia. In the AGA guideline, TIPS is recommended as the first option when medical and endoscopic approaches fail [60]. This technique has made mechanical portal decompression popularized again in the treatment of

portal hypertension. However, there are no data supporting the use of TIPS for primary prophylaxis of variceal bleeding [60]. Considering the insufficient data and TIPS-related complications (high risk for hepatic encephalopathy), it is not recommended for primary prophylaxis of variceal bleeding [60, 70].

Extrahepatic portal vein occlusion (EHPO) is a disease characterized by portal hypertension, severe esophageal variceal bleeding, and splenomegaly. Liver functions are usually within normal limits. Non-cirrhotic portal is the most important cause of hypertension in children. There is very little data on medical and endoscopic approaches in the treatment of extra venous obstructions in children, and surgical prophylaxis is recommended [61]. For this purpose, Meso-Rex bypass is recommended [62]. Pal et al. (2013) performed prophylactic splenorenal shunt in 98 cases and esophagogastric devascularization in 16 cases in their 114 case series.

Cirrhosis is the most important cause (80%) of ***ectopic varicose veins*** detected in the small intestines, colon, and rectum, other than the esophagus. The first treatment option to be used for prophylactic or definitive treatment is endoscopic approaches such as band ligation and sclerotherapy [71].

9.4.2 Locally Invasive Gallbladder Tumors

In 0.3–3% of cases undergoing laparoscopic cholecystectomy, gall bladder carcinoma is detected. In T1a cases, laparoscopic cholecystectomy is sufficient (see Chap. 11). The risk of vascular and perineural invasion increases in the lesions reaching the subserosis, and lymph node involvement is detected in approximately half of the cases [72]. In T1b cases, radical cholecystectomy should be performed. In T2 cases, segment 4B and five parts are included in the resection. Kwon et al. (2020) stated that there was no significant difference in survival between segment 4–5 resection and wedge resections in the T2 series. In the same series, survival in T2a (peritoneal side) lesions was found to be better than T2b (hepatic side) lesions [73]. The cystic canal stump sampling should be done with frozen section. Extrahepatic biliary tract resection and regional lymph node dissection are also performed in cases with tumor-positive results. Combination therapies with multidisciplinary approach should be applied in T3 and T4 cases. In T3 cases, Caudate lobe resection and lymph dissection and resection in the affected tissues should be performed in addition to the extended right or left hepatectomies [74].

9.4.3 Hydatid Cyst

Echinococcus granulosus and *Echinococcus multilocularis* (alveolaris) cause hydatid cysts and alveolar hydatid cysts in humans. Perforation of the cyst into the biliary tract is the most common complication in patients with hydatid cyst. Cysts that are fistulized to the biliary tract change the treatment algorithm. In these patients, the results obtained after sphincterotomy and stenting with ERCP will determine the extent of the operation to be performed. Another important cause of morbidity and mortality encountered after hydatid cyst surgery is the development of a bile fistula (leak). In cases where bile fistula is detected, endoscopic sphincterotomy, stent application, or nasobiliary drainage can prevent the pressure in the biliary tract and flow of bile into the cyst cavity. In patients who underwent prophylactic endoscopic sphincterotomy, fistula incidence decreases, and the duration of hospitalization is shortened [75, 76]. Çiçek et al. (2007), in a study involving 69 patients who underwent hydatid cyst surgery and developed bile fistula, reported that all patients were successfully treated with endoscopic sphincterotomy and stenting [75].

Alveolar hydatid cysts form a lesion that covers the liver in a period of approximately 20 years and disrupt functions with signs of compression [77]. Prophylactic resections can be performed in cases where partial control can be achieved with the use of albendazole or liver reserve is sufficient (Fig. 9.3).

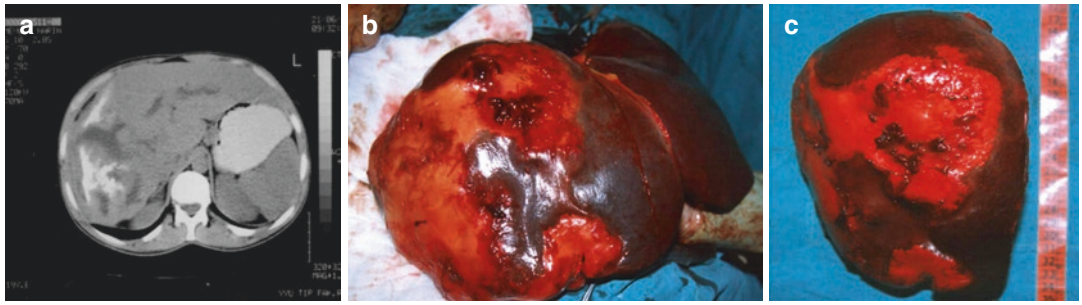

Fig. 9.3 In this picture, CT image (**a**) and surgical specimen (**b**, **c**) of our patient who had a right hepatectomy 23 years ago due to an alveolar hydatid cyst are still living healthy

9.4.4 Liver Traumas

The liver is the most frequently injured intraabdominal organ. In hemodynamically stable injuries, most of the cases will recover with close follow-up of the patient (Laboratory, USG-FAST, and CT). In 50–85% of cases with liver trauma, bleeding stops spontaneously [78–80]. Complications such as hemobilia, hematoma, and biloma that may be encountered in the healing process can be successfully treated with interventional radiological procedures. Angiography and embolization can also contribute to diagnosis and treatment in liver injuries.

Approximately 14% of patients with liver injuries require surgical intervention [80, 81]. Operative management of liver injuries in severe injuries can be difficult even for experienced surgeons due to the complex nature of the liver, its size, vascularity, blood supply, and hard-to-reach venous drainage. The aim of the surgeon should primarily be to provide hemodynamic stabilization of the patient. A definitive procedure can be applied in experienced centers. However, short-term Pringle maneuver can be performed to control bleeding in severe liver injuries detected in patients who are hemodynamically unstable and laparotomized. In case of lack of experience, bleeding can be temporarily taken under control by packing. At the time gained, the patient can be transferred to an experienced center or depacking after 24–48 h.

After liver injury and other intra-abdominal injuries are managed, the abdomen can be closed, but open abdominal management should be kept in mind as a risk-reducing method due to the risk of abdominal compartment syndrome and the need for a second look.

9.4.5 Hepatolithiasis

Hepatolithiasis is an endemic entity in many countries, especially in the Far East. Its incidence varies between 4 and 52% [82]. In some countries, it is a serious public health problem due to its causes and consequences. Stone formation in the liver can occur in many cases where bile flow is blocked or slowed. Chronic inflammation develops as a result of recurrent cholangitis attacks in patients who develop bile duct stenosis and cholestasis, and this causes hyperplasic changes in the mucosa. With the prolonged inflammatory process (10–20 years), cholangiocarcinoma develops in 10% of cases [83]. In the treatment of hepatolithiasis, first endoscopic methods and medical approaches should be applied. Prophylactic liver resections (Fig. 9.4) or biliary drainage procedures should be performed when treatment is inadequate [82].

9.5 Miscellaneous Procedures

9.5.1 Transplantation

Liver transplantation is one of the procedures that have been standardized today and successfully performed by transplantation surgeons in hepatobiliary centers. Liver transplantation can

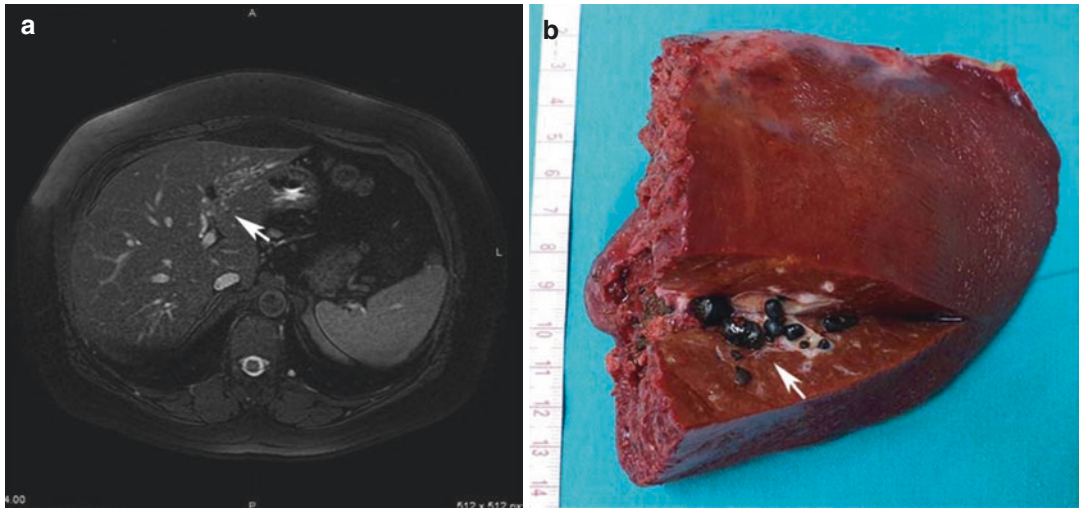

Fig. 9.4 CT image (**a**) of a patient with hepatolithiasis shows a large number of stone images (Arrows) seen in the lateral sector. A large number of gallstones are seen in the patient's resected specimen (**b**)

be done for various reasons for preemptive purposes. Today, some of the patients who cause biliary stenosis and are followed up with recurrent cholangitis have a risk of developing cirrhosis, portal hypertension, and ultimately cholangiocarcinoma [84, 85]. Segmented resections should be performed first in patients with followed choledochal cysts and Caroli's disease. If the disease cannot be controlled and complications develop, preemptive transplantation is the last option [86]. In patients with biliary atresia, hepatoportoenterostomy should be performed primarily. In patients with biliary atresia, the anatomy is very small and technical difficulties reduce the success of transplantation, approximately 2–3 years can be saved with portoenterostomy and the chance of success in transplantation in growing children increases. Transplantation seems to be the most effective method in patients with primary sclerosing cholangitis.

9.5.2 Portoenterostomy

Hepatoportoenterostomy is the standard treatment procedure for biliary atresia (Cox 2014). If this technique is successful, approximately 50% of patients with biliary atresia can eliminate or delay the need for liver transplantation (Schreiber). If the technique is not successful or if stenosis develops in the early postoperative period, transplantation is recommended instead of revision surgery [39].

There is very little literature data about the indications of portoenterostomy except biliary atresia [87–90]. In cases where hilar dissection is performed in extrahepatic biliary tract and Klatskin tumors and hepatectomy cannot be performed, or after major biliary tract trauma, portoenterostomy can be performed in multiple segmental biliary tract reconstruction [90].

Anastomosis is started with sutures between the portal vein side, the jejunum, and the lateral wall of the bile duct (Fig. 9.5). In the gaps between the corner and ductus sutures, hilar plate (liver tissue) and sutures passing through the jejunum are used [90]. Roux-en-Y type anastomosis should be preferred to avoid postoperative recurrent cholangitis.

Portoenterostomy instead of hepaticojejunostomy in small and multiple biliary radicles and bile duct cancers should be performed in selected patients. In the presence of active inflammation, fibrosis, major bile duct trauma, and thin bile duct radicles, this method provides an excellent salvage surgical procedure with less morbidity.

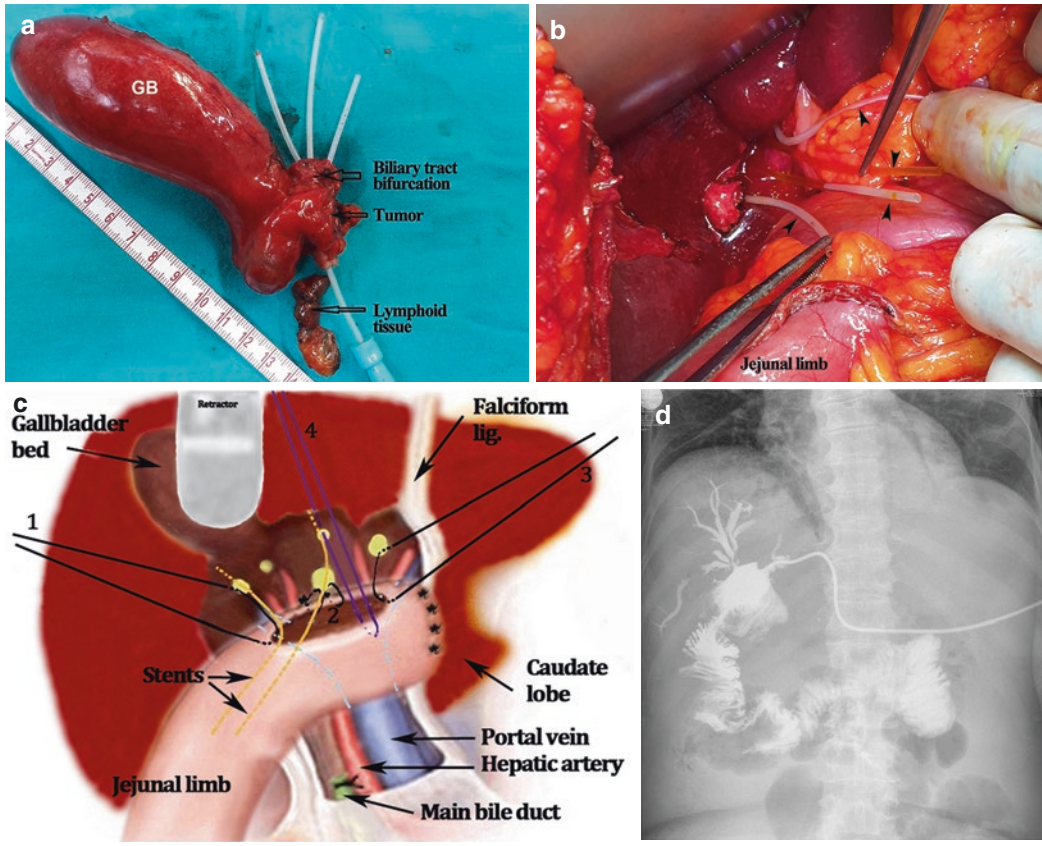

Fig. 9.5 A portoenterostomy can contribute in cases where a large number of bile ducts appear after hilar dissection (**a**, **b**) or trauma. Figure (**c**) shows the illustration of portoenterostomy. Figure (**d**) shows the patency of portoenterostomy including multiple duct ends. (Figure **a**, **b**, and **c** taken from the article of Dilek et al. in the 2020 issue of Indian J Surgery)

9.5.3 Portal Vein Embolization (PVE)

One of the biggest problems in patients undergoing right hepatectomy is liver failure after resection. PVE is recommended when the resection can exceed 50–60% (Fig. 9.6). It is an application developed by Makuuchi et al. (2004) [91]. In order to reduce the risk of insufficiency by making the left lobe hypertrophic, the right portal vein is occluded with coils or embolizing agent, and after 15 days, hypertrophy is expected to develop in the left lobe [91, 92]. In the series of Nagino et al. (2006), which published one of the largest series in the literature, the 8.8% mor-

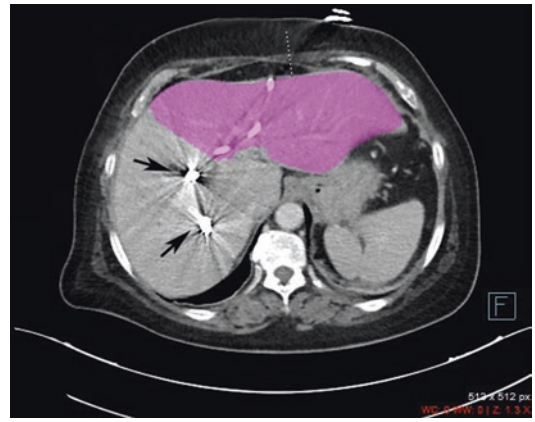

Fig. 9.6 PVE increases the chance of resection and reduces the risk of failure

tality rate seen in patients with resection without PVE decreased to 4.5% in those operated after PVE [93]. In the series of Hemming et al. (2005), the rates were reported as 21% and 3%, respectively [94]. However, in the series of Farges et al. (2003), there was no significant difference between them [95]. In our own clinical practice, we perform routine PVE in cases where we think the left lobe will be insufficient.

9.5.4 Caudate Lobe Resection

Removal of the Caudate lobe is recommended in biliary tract carcinomas (Klatskin tumor) with hilar location [92, 96]. The addition of Caudate lobe resection to hepatectomy reduces local recurrence and provides long survival. Mizumoto et al. (1986) demonstrated the presence of tumors in the Caudate lobe in 11 cases in 24 case resection series [97]. Nimura et al. (1990) reported a 5-year survival as 40.5% in the series where they performed a Caudate lobe resection with hilar lesion due to hilar cholangiocarcinoma [96, 98]. Caudate lobe resection is widely practiced in Japan.

9.5.5 Pringle Maneuver

The "hepatic inflow occlusion" maneuver described by Pringle from Glasgow for the first time in 1908 due to liver trauma is a method that is frequently used today [99]. The intermittent form of the Pringle maneuver is more preferred.

Intermittent Pringle maneuver can be used in deeply located pathologies and in cases where large vascular resection is required, and in cases where the vena cava is invasive, total vascular exclusion techniques are preferred. Where the procedure is prolonged, hypothermic perfusion should be supported by mesenteric vascular bypass, pharmacological intervention, and ischemic preconditioning to prevent (reduce) ischemia/reperfusion injury [100].

Simultaneous clamping of the portal vascular structures (Pringle maneuver) can also be performed by placing a vascular clamp along the hepatoduodenal ligament or compressing it with a silicone loop.

9.5.6 Perihepatic Packing

The procedure to be performed in patients with liver trauma and hemodynamically unstable is primarily stabilizing the patient in terms of hemodynamics. For this purpose, Pringle maneuvering and packing are the first things that come to mind. Perihepatic packing has been a basic technique to control bleeding after liver traumas in the last two or three decades. Some studies have left question marks about its effectiveness. However, the perihepatic packing technique is reported to reduce bleeding and mortality and can be life-saving [101, 102]. Packing is an auxiliary procedure in preserving the integrity of the liver and keeping the hemodynamics stable and may save time on transfer to an experienced center.

Perihepatic packing technique: It involves compressing the liberated liver between compresses and the diaphragm, abdominal wall and colon [101]. Intrahepatic packing is not recommended as it may increase injury and bleeding [103]. After first packing and haemodynamic stability, packing structures should be removed. If the bleeding continues when the packing structures are removed, it should be considered to carefully replace the packing structures and temporarily close the abdominal wall for a second look (Fig. 9.7). The packing structures are removed (depacking) 24–48 h later [101].

All trauma surgeons in the world do not work under the same conditions, they do not have the same opportunities and technologies [78]. In insufficient conditions, perihepatic packing can be a time-saving technique for transferring the patient to a higher center. However, in cases where bleeding control cannot be achieved with perihepatic packing, more aggressive techniques should definitely be considered [101].

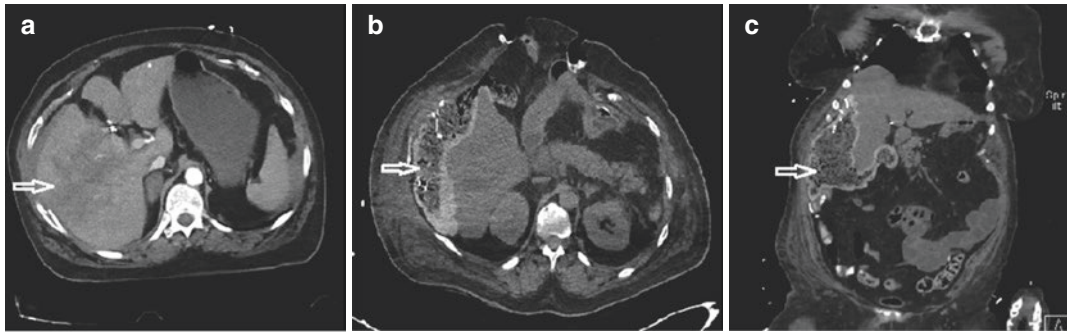

Fig. 9.7 Abdominal CT images of the packing (**b**, **c**) technique (Arrows) we applied in a patient with grade 5 liver trauma (**a**)

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Prophylactic Resections of the Pancreas Pathologies

10

Osman Nuri Dilek and Turan Acar

10.1 Introduction

The pancreas, which was understood to be a secretory organ in the 1640s, began to perform partial resections in animals in the 1660s. In 1679, Bonet from Genova identified the first pancreatic tumor [1]. However, it remained a mysterious and incomprehensible organ until the mid-nineteenth century. Wandesleben, who was a doctor in a small German town, made his first pseudocyst drainage and the first pancreatic surgical intervention in 1841 [2, 3]. This was followed in 1881 by Rokitansky's partial resection, which resulted in death. In the same year, Bozeman performed the first successful cyst resection in New York. This was followed by Trendelenburg's first successful distal pancreatectomy operation in Germany in 1882 due to the tumor. Billroth performed the first central pancreatectomy in 1885. Ruggi from Bologna made first successful enucleation in 1889. By 1900, 177 pancreatic surgeries were reported [1]. These were followed by Gordon-Taylor's (1927) subtotal pancreatectomy with portal vein resection surgery, Brunschwig's (1937) pylorus-preserving pancreatoduodenectomy surgery, and Whipple's (1940) pancreatoduodenectomy with antrectomy surgeries [4].

Pancreatic surgery has been one of the addresses of the most challenging interventions in surgery due to its organ location, neighborhood, and high perioperative morbidity. The pancreas can be defined as "*an organ that God hides from surgeons*" by its location. Today, pancreatic surgeries are performed with open, laparoscopic, or robotic methods with the development of information and technological opportunities related to diagnostic and therapeutic procedures. Besides, many pancreatic pathologies can be treated without the need for surgery, with endoscopic and radiological interventional methods.

In this section, the place of prophylactic surgery in hereditary pancreatic tumors, cystic neoplasms, premalignant lesions with benign character, and miscellaneous conditions is going to be evaluated.

10.2 Pancreatic Neoplasms

Pancreatic cancers are generally asymptomatic and the deadliest cancers (Goral). Early diagnosis and management are the most important factors in the success of treatment. Currently, more diagnoses of hereditary pancreatic tumors and precancerous cystic lesions have been made, and

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in the follow-up, interventional procedures have started to play an important role in addition to total pancreatectomy (TP), pancreaticoduodenectomy (PD, Whipple procedure), and central or distal pancreatectomy (DP).

10.2.1 Familial Pancreatic Cancer

Pancreatic cancer may develop as sporadic (90%), familial (7%), or hereditary (3%) [4]. Familial pancreatic cancer has been defined by consensus opinion as: families with two or more first-degree relatives with pancreatic cancer who do not meet criteria for a known pancreatic cancer-associated hereditary syndrome [5, 6]. The risks for affected individuals with affected 1, 2, and 3 family members are 4.6, 6.4, and 32-fold, respectively [7, 8]. Besides the genetics, there are also exogenic risk factors in the development of familial pancreatic cancer including, smoking and environmental factors, and also different hereditary diseases such as polyposis syndromes such as Peutz-Jeghers, hereditary pancreatitis, familial atypical mole melanoma syndrome (FAMMM), hereditary breast and ovarian cancers, and hereditary non-polyposis colon cancer (HNPCC) [9–11].

It is still controversial how and how often these high-risk individuals should be screened, whether the screening will detect an "early" malignancy, and when to consider prophylactic pancreatectomy. The utilization of screening for detection is expensive, insensitive, and depends on the detectability of the mass. Generally, it is recommended to start screening at the age of 40 or 10 years younger than the youngest relative with pancreatic cancer [12]. There is a consensus on that endoscopic ultrasonography (EUS) or MRCP will be the best initial screening method with an approximate accuracy rate of 43% [13]. Successful screening targets are early invasive pancreatic cancer and intraductal papillary mucinous neoplasms (IPMNs) or pancreatic intraepithelial neoplasia (PanIN) with high-grade dysplasia, which may be treated early (prophylactic) surgically with curative intent [14]. The characteristics of pancreatic histology in familial pancreatic cancer kindred are multifocal PanINs or IPMNs associated with duct ectasia and parenchymal atrophy [15].

The degree of resection is controversial in terms of therapeutic concept. While prophylactic pancreatectomy was performed in these patients formerly, it is not preferred today due to the high morbidity and mortality rates and also uncontrolled diabetes [16, 17]. A completion pancreatectomy for the remaining pancreas can be performed without increasing the morbidity and mortality, so the main goal is removal of all precancerous lesions or resection of a targeted area containing only nodular or cystic lesions [18–20]. Also, there are publications recommending TP with islet autotransplantation, but larger series are needed [21, 22].

10.2.2 Pancreatic Neuroendocrine Tumors

Incidence of pancreatic neuroendocrine tumors (panNETs) has increased in recent years; however, it constitutes 7% of all neuroendocrine tumors and 1–2% of pancreatic lesions [4, 5]. They are classified according to their hormone secretion capabilities as functional (10–50%) or nonfunctional (50–90%) (NF-panNETs) [6].

Although magnetic resonance imaging (MRI) is superior to computerized tomography (CT) in the diagnosis of panNETs, both methods should be utilized for operability. Endoscopic ultrasound is not required to determine the surgical resectability, but EUS-FNA can be applied to confirm the diagnosis in equivocal cases or to determine the tumor grade [7].

While surgery is the standard treatment in functional or large panNETs, optimal management of small NF-panNETs is still controversial because of the absence of large prospective randomized trials, and variable clinical symptoms and prognosis. There are some studies suggesting prophylactic surgery for all panNETs [8]. However, many studies report that observation is a safe method in small and NF-panNETs [9, 10]. The National Comprehensive Cancer Network (NCCN) states that observation can be considered for low-grade, incidentally discov-

ered NF-panNETs <1 cm in size [14]. Assi et al., in their study from 2020, reported that in patients with lesions 1–2 cm and >2 cm, the rate of over survival was better when surgery was performed, so that NF-panNETs smaller than 1 cm could be followed but surgical resection should be preferred in larger ones [16, 23].

On the other hand, according to The North American Neuroendocrine Tumor Society (ENETS) Consensus published in 2020, observation should be primary strategy in asymptomatic NF-panNETs smaller than 1 cm and confirmed by imaging [15]. The choice of observation or resection of the lesions between 1 and 2 cm should be decided according to the individuals. Criteria that should be considered in decision-making include age and comorbidities, tumor growth over time, estimated risk of symptom development, details of imaging, grade, the extent of surgical resection required, the patient's wishes, and access to long-term follow-up.

Depending on the localization of the lesion and its relation with the duct, open/laparoscopic or robotic enucleation, PD or DP can be performed in patient candidates for surgery [17, 18].

10.2.3 MEN Syndromes

The risk of developing pNET during the 30-, 50-, and 70-year follow-ups of MEN-1 syndrome patients with the MEN1 mutation has been reported as 45%, 82%, and 96%, respectively [24]. In other words, pNET develops in 40–75% of the patients with MEN-1 syndrome. Gastrinomas can also be encountered at any age group in patients with MEN-1 syndrome [25].

According to ATA criteria, follow-up should be started at the age of 11 in patients with high-risk allele and at the age of 16 in those with moderate risk. Plasma-free metanephrine, plasma nor-methanephrine, and urine nor-methanephrine levels should be monitored during the follow-up. Individuals with unremarkable hormone levels may need to be scanned with MRI and/or CT. Alpha adrenergic blocker should have been administered before the surgery to avoid a hypertension crisis during the operation.

Hormones that are synthesized in cases with the known hereditary cancer syndromes can be utilized as a disease-specific marker [26].

10.3 Cystic Neoplasms and Precursor Lesions

Pancreatic cystic lesions (PCL) are more frequently encountered by the advances of the imaging methods (such as CT and MRI) and EUS and their increased utilization. Although the precise prevalence of cystic lesions is unknown, it has been reported in different series at rates ranging from 1.9 to 49.1% [4, 5, 8]. About 40–70% of PCL do not give any clinical signs because they grow very slowly [6, 7]. Most of the cases are detected incidentally. Although about 20 cystic lesions defined histopathologically in the pancreas (Fig. 10.1), 95% of cases are serous cystic neoplasms, mucinous cystic neoplasms, IPMNs, and solid pseudopapillary tumors.

Resection is recommended for solid pseudopapillary tumors that have a slow course but have malignant potential [27]. When the guidelines were reviewed, surgery was reported to be gold standard treatment in PCLs with malignant character, while different treatment approaches were reported in benign and borderline cases [9–11]. In addition to those who advocate early surgery (prophylactic surgery), there are also researchers who state that successful results were obtained with close surveillance.

10.3.1 Serous Cystic Neoplasms

Serous cystadenomas (SCAs) are benign tumors that account for 10–29% of PCLs and 1–2% of all pancreatic neoplasms [9, 10]. These cysts are rich in glycogen and can be composed of single large (oligocystic) or numerous microcysts (polycystic), located around a calcified center, containing clear fluid in the form of a honeycomb, characterized by septations and thick fibrous walls. Aggressive spread (distant metastasis) is rare even in malignant forms and they are mostly locally invasive [5, 6]. SCAs are more common

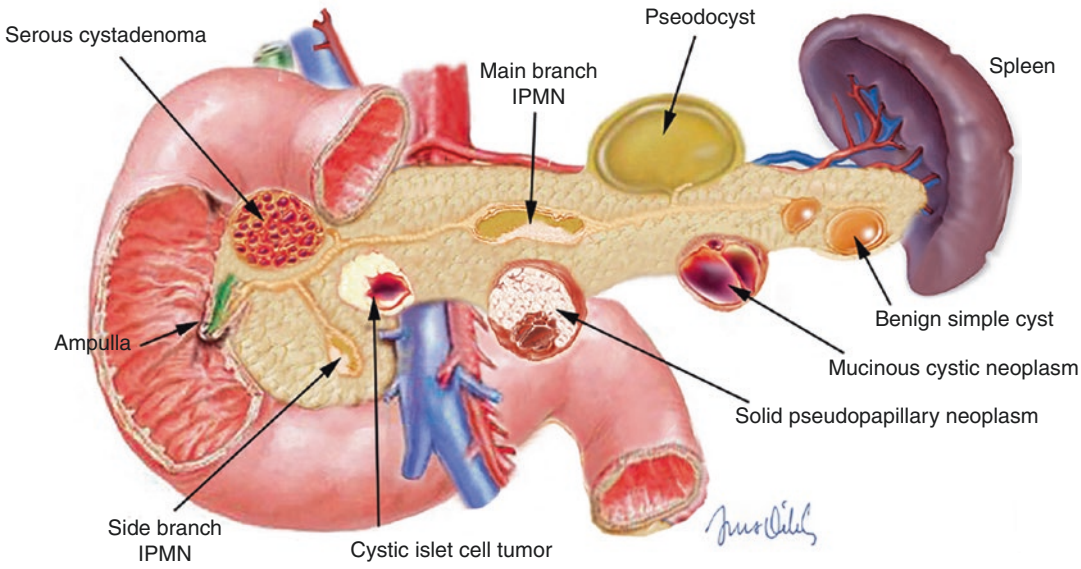

Fig. 10.1 The most common PCLs and their most common localizations

among women (77.8%) and sixth and seventh decades [11, 12]. SCAs can be localized in the entire parts of the pancreas [16]. Mean diameter is about 5–6 cm, and cases growing up to 25 cm have been reported [17]. SCAs are associated with von Hippel-Lindau (VHL) disease and with many sporadic tumors [15]. It is very important to differentiate SCA from other cystic neoplasms in order to manage it properly [19]. Although CT enables accurate diagnosis in typical cases, it is difficult to distinguish especially macrocystic and oligocystic ones from MCA [21]. In such cases, MRI with T2-weighted sequences increases the diagnostic value [22].

In current guidelines, EUS and/or EUS-FNA are recommended in addition to other imaging methods to obtain more data in the definitive or differential diagnosis and to select patients who are candidates for surgical resection (GRADE 2C, strong agreement) [28, 29]. EUS-FNA is particularly effective in assessing the presence of mucin in the lesion (GRADE 2C, strong agreement) [30]. Additionally, histological examination, DNA molecular analysis, and measurement of amylase and tumor markers (especially CEA and Ca 19-9) can be performed from EUS-FNA cyst fluid [16, 31]. If contrasted EUS is used, the vascularity of the wall nodules and cyst septations can be evaluated more sensitively (GRADE 2C, strong agreement) [32]. However, despite all these developments, the accuracy of the preoperative diagnosis is still between 47 and 78% [20].

Although there is no specific symptom related with SCA, it may cause early satiety, obstructive jaundice, abdominal mass, vomiting, nausea, weight loss, and pain depending on the localization of the lesion in pancreas [13, 14]. Despite the fact that the vast majority of patients are asymptomatic, due to the difficulties in definitive diagnosis, discussions on follow-up and prophylactic-curative surgical treatment are still ongoing and there is no standard treatment.

The general opinion is that the follow-up with conservative treatment would be more favorable in cases when radiological and/or endoscopic findings are characterized for SCA, since the advantage of resection (the incidence of malignancy is very low) will not be better than the burden of postoperative complications and long-term outcomes of metabolic digestion [33–35]. One of the most recent studies on this issue belongs to El-Hayek et al. (2013), in which they followed 194 (89%) of 219 patients with SCA nonoperatively and operated 25 patients with symptom-

atic disease or suspicious diagnosis [11, 36]. As a result of long observation, they reported that asymptomatic patients had a very slow growth pattern and did not present any symptoms, so nonoperative follow-up was found to be appropriate. In cases of large size and considered for nonsurgical approach, percutaneous drainage of the cyst fluid can be performed, but it has no place in curative treatment. Many interventional procedures for prophylactic purposes will be described in detail in Chaps. 40 and 42.

Tariq et al. (2018) reported that conservative approach would be sufficient in the most cases, but it is not always possible to access radiological-endoscopic interventions for preoperative differential diagnosis, and surgery may be the first choice in developing countries like them [34]. However, prophylactic-curative surgery should be performed in cases with large lesion (≥4 cm), young age, severe symptoms, or presence of solid components, vague diagnosis, or malignant appearance despite extensive studies (CT, MRI, EUS/EUS-FNA) [37–40]. In these patients, Whipple procedure, central pancreatectomy, distal pancreatectomy (with splenectomy or spleen preserving), or, if appropriate, less invasive procedures such as enucleation can be performed. There is no need for lymph node dissection.

Distant metastasis or recurrence after resection in remnant tissue has not been reported. Therefore, long-term follow-up is not required in SCAs that are pathologically confirmed and surgically completely resected. SCA patients in whom resection was not or could not be performed should be monitored every 6 months in first 2 years, followed by annual CT or MRI [41].

10.3.2 Mucinous Cystic Neoplasms

Mucinous cystic neoplasms (MCN) accounts for 2–5% of all PCLs [4]. According to the criteria of The World Health Organization (WHO), MCNs are cystic tumors located ectopically into the pancreas during embryogenesis, surrounded by ovarian-type stroma, containing mucin-producing columnar epithelium and not associated with the pancreatic duct [5]. The 2004 International Association of Pancreatology made the presence of an ovarian stroma mandatory for the diagnosis of MCN [9]. The vast majority have been single lesions, and only a handful of isolated cases with multiple—usually double—lesions exist [6]. Approximately 80% of the patients are women, mostly in middle ages and located in the distal pancreas (body-tail) [7]. The presence of any macrocystic lesion in the distal pancreas of a female patient should bring MCN to mind. The mean diameter is 5 cm (2–25 cm) and despite its distal location, it is frequently symptomatic at the time of diagnosis (76%) [8].

Malignancy risk of MCN varies between 6 and 36%. Clinical factors that contribute this risk are not well described. However, advanced age, presence of septations, large cyst size, and presence of mural nodularity are considered to increase the risk of malignancy [10].

MCNs appear as hypovascular septal cysts with well-circumscribed, thick, and irregular walls on US, CT, and MRI. EUS imaging alone was accurate for diagnosing a benign from a malignant cyst 65–96% of the time, and papillary epithelial protrusions extending into the cyst (solid component) are better determined [11]. The cytology obtained by EUS-FNA in cyst fluid is highly specific (83–100%), but it is relatively insensitive (27–48%), resulting in low diagnostic accuracy (8–59%) [12, 13].

Analysis of pancreatic cyst fluid has been shown to aid the differential diagnosis of mucinous and non-mucinous lesions (using a CEA cutoff of 192 mg/dL and amylase) [15]. Unfortunately, CEA level does not provide information about the risk of malignancy. It can be usually confused with pseudocyst and Intraductal Papillary Mucinous Neoplasms (IPMN). In this case, differential diagnosis can be made by searching the presence of an inflammatory reaction which is seen around the pseudocysts and the presence of pancreatic ductal involvement in IPMN, unlike MCN [14].

A multidisciplinary approach is required for treatment management. The general opinion is that since MCN has a high malignant potential, prophylactic-curative surgical resection with low

morbidity rates should be performed [18–20]. However, depending on the size and radiographic features, the number of those who advocate close follow-up is quite much to underestimate [16, 17].

Two important guidelines European evidence-based guidelines and The American college of gastroenterology (ACGG) published in 2018 made important recommendations regarding surgical resection criteria in MCN. According to European evidence-based guidelines published in 2018: cyst size ≥40 mm, symptomatic, and mural nodules are definitive indications for surgery [11, 21]. According to The American college of gastroenterology (ACG) guideline published in 2020: jaundice (tumor-related), acute pancreatitis (AP) (tumor-related), elevated serum Ca 19-9 when no benign cause for elevation is present, mural nodule, or solid component within the cyst or pancreatic parenchyma, main pancreatic duct diameter of >5 mm, change in main duct caliber with upstream atrophy, size >3 cm, increase in cyst size >3 mm/year are definitive indications for surgery [22]. In many centers, early (prophylactic) surgical resection is performed to high-risk patients without invasive cancer or high-grade dysplasia in line with these guidelines.

10.3.3 Intraductal Papillary Mucinous Neoplasms

Intraductal papillary mucinous neoplasms (IPMNs), first classified by WHO in 1996, are epithelial tumors caused by ductal dilatation due to mucin production, from the main pancreatic duct or/and ductal branches (Fig. 10.1) [4]. IPMN is slightly more common in males, the peak incidence ranges from 60 to 70 years, and the risk of IPMN development and malignant degeneration has been reported to increase with age [30]. Other risk factors include lifestyle, smoking and alcohol abuse, increased body mass index (BMI), abdominal fat, diabetes mellitus (DM), and family history [31–33].

It is believed that IPMN is a process involving the entire pancreas, there are three subtypes depending on the localization and extent of the lesion: Main duct (MD-IPMN), branch duct (BD-IPMN), and mixed-type IPMN (MT-IPMN) [5]. Each subtype has a certain risk of malignancy and requires a specific therapeutic approach. MD-IPMN is recognized as dilation (segmental or diffuse) of the main pancreatic duct (MPD) of >5 mm and accounts for 15–21% of all IPMNs [6, 7]. It is mostly observed in pancreatic head localization (64–67%) and 70% is symptomatic [8]. It has a high risk to exhibit malignant disease (28–81%) [42]. BD-IPMN is defined as bunch-shaped dilation (>5 mm) in lateral channels [11, 12]. It accounts for 41–64% of IPMNs and can be found throughout the entire pancreas more frequently in the uncinate process [13, 14]. The risk of malignancy is lower than other types (7–42%), and young age and new-onset diabetes mellitus are considered as poor prognostic factors [42]. There are risks of multifocality (40%) and high recurrence (7–8%) after surgery. MT-IPMN is seen in 20–65%, meets both MD and BD-IPMN criteria, and has a malignancy risk of 22–38% [17, 18].

Most of the patients are asymptomatic, and depending on the localization of the mass, symptoms such as jaundice, abdominal pain, secondary acute (recurrent) pancreatitis, weight loss, steatorrhea, and back pain can occur in advanced and invasive tumors [34, 35, 37, 38].

Despite advances and increasing accessibility in radiological methods, diagnosing IPMN is still complicated [43]. In the study by Lekkerkerker et al. [39], while preoperative diagnosis was correct in 80% of BD-IPMNs and 89% of MD/MT-IPMNs [39], in another high-volume center, preoperative diagnosis was false in one-third of cases and 20% of the estimated BD-IPMNs had main canal involvement in postoperative histology [11]. Generally, MRI (combined with MRCP) is the preferred method because of its superiority in identifying cyst differentiation and its connection to the main ductal canal, mural nodules and septations [40, 41, 44]. CT is, on the other hand, recommended for the classification of calcifications, staging of the tumor, or postoperative follow-up [45].

EUS is a good alternative imaging method. It is mainly used to assess the presence of alarming features. While it has a low accuracy for differen-

tiation between cyst types, it is quite suitable for the recognition and identification of malignant features, especially intracystic structures [46–49]. A 98% mural nodule can be detected with contrast EUS [42]. The biggest advantage of EUS is that it can make FNA simultaneously. EUS-FNA is indicated in the case of uncertain imaging findings [50]. The American Gastroenterological Association (AGA) recommends EUS-FNA in patients with cyst diameter of 3 cm, solid component or dilated main pancreatic duct (MPD) [51–53]. Cytological analysis of cyst fluid has high specificity (91%) but low sensitivity (65%) to differentiate benign and malign IPMN [54, 55].

Contrast-enhanced EUS can detect mural nodule with the rate of 98% [49]. The biggest advantage of EUS is that simultaneous FNA can be performed. EUS-FNA is indicated in the case of unclear imaging findings [50]. AGA recommends EUS-FNA in cases with cyst diameter of 3 cm, having solid component or dilated MPD [51, 52, 56].

PET/CT may also be useful in the management of patients, especially those who have high risk for surgery [57].

Although the malignancy risk of IPMNs is high, the treatment algorithm is still controversial (especially on BD-IPMN) and there are only periodically revised national and international guidelines [21, 22, 28, 29, 58–61]. In all guidelines, life expectancy and comorbidity have been firstly taken into consideration, and increased wall thickness, mural nodule, and increase in solid component were reported to raise the risk of malignant disease. MPD dilation is one of the main criterion for surgical indication, and some guidelines accept 10 mm as the cutoff value for surgery [11, 56, 62–64]. Although cyst size is associated with the risk of invasive cancer, there is no definitive judgment regarding that small cysts are either not malignant or large cysts will be malignant [64]. Hwang et al. (2020) in their work evaluating the guidelines reported that enhancing mural nodule ≥5 mm, increased serum Carbohydrate Antigen 19-9 (Ca 19-9), MPD diameter ≥10 mm, acute pancreatitis, and their combinations could be helpful to predict the malignant potential of IPMN [61].

Since MD-IPMN and MT-IPMN have a higher risk of malignancy than BD-IPMN, more aggressive surgery should be performed. Depending on the localization of the cyst, open/laparoscopic or robot-assisted PD (42–70%) and DP with or without spleen preservation (13–47%) can be performed [65, 66]. Due to the risk of decreased quality of life, TP is recommended only when there are more than one malignant-looking cysts throughout the entire pancreas, or there is a recurrence in remnant pancreatic tissue [67, 68]. Coco et al. (2019) concluded that multiple IPMNs are the most suitable indications for TP [69].

In selected BD-IPMNs, pancreatic protective procedures such as enucleation, central pancreatectomy, and resection of the uncinate process can be performed in order to maintain exocrine and endocrine pancreatic function [70].

After these surgical interventions, complications such as leak, stenosis, fistula, intraabdominal abscess, pancreatitis, pseudocyst, cholangitis, gastric emptying disorders, diarrhea, and pneumonia may develop with the rate of 25% [71]. To minimize this rate, those interventions should be performed in high-volume centers, by highly experienced surgeons and after a multidisciplinary approach [72]. Lee et al. (2010) reported that 16 patients undergoing prophylactic pancreatectomy did not have anxiety and problems related to quality of life (QoL) [33].

Since the presence of positive margin is the most significant cause of poor prognosis, an intraoperative frozen section analysis should be performed in order to evaluate any signs of high-grade dysplasia or an occult invasive cancer [73].

Although IPMN-related cancers generally have better oncological outcomes, if any of the poor prognostic factors exist, the result is similar to cases with ductal adenocarcinoma. The greatest risks in terms of postoperative mortality are comorbid disease and advanced age [74–76]. Performed a meta-analysis and found a disease-specific mortality of 23 for all IPMN, 32 for MD-IPMN, and 5 for BD-IPMN per 1000 patient years [76].

Lifelong follow-up is recommended after resection, due to the risk of formation of a new lesion or distant metastasis [77, 78].

10.4 Miscellaneous Conditions

10.4.1 Pseudocysts

Pancreatic pseudocysts (PPC) are the most common pancreatic cystic lesions [4]. They usually develop on the background of acute or chronic pancreatitis [13, 14]. They occur with mild symptoms such as pain, abdominal fullness, nausea, vomiting, and jaundice, and they manifest biochemically radiologically specific signs [5, 15]. While CT is an adequate imaging method for the detection [16], MRI/MRCP is the most preferred method for definitive diagnosis since it is able to display the relation of the pseudocyst with the pancreatic duct [15, 16]. In addition, differential diagnosis from other PCLs can be made by analyzing the cyst fluid taken with EUS-FNA [8, 13].

Most PPCs are asymptomatic and do not require any treatment, more than 90% of small pseudocysts (<5 cm) are expected to recover spontaneously. Forty percent of newly formed PPCs disappear spontaneously after 6–8 weeks of waiting and watching. However, some PPCs require endoscopic or prophylactic/curative surgical intervention [14]. The conventional approach is transgastric endoscopic interventions accompanied by EUS [10, 22]. However, when endoscopic procedures are inadequate or unsuccessful, surgery is required. The main indications for surgery are: complicated pseudocysts (i.e., infected and necrotic pseudocysts), pseudocysts associated with pancreatic duct stricture and a dilated pancreatic duct, suspected cystic neoplasia, coexistence of pseudocysts and bile duct stenosis, and complications such as compression of the stomach or the duodenum, perforation and hemorrhage due to erosion of arteries or pseudoaneurysms [11].

Drainage procedures are the basis of surgery. These include external drainage, internal drainage, and excision [12]. Usually, external drainage is not a preferred method due to the risk of fistula. Cystoduodenostomy can be performed when the cyst is located in the head and uncinate of the pancreas. Roux-en-Y cystojejunostomy, on the other hand, can be preferred in all types of cysts [13].

Surgical resection was used as an alternative approach for PPCs, and indications for this procedure included cystic neoplasia, splenic vein involvement, upper gastrointestinal bleeding, and technical inability to drain a pseudocyst located in the uncinate [17, 19]. PD, DP, or TP can be performed in these patients according to the localization of the lesions and also malignancy risk [16].

10.4.2 Chronic Pancreatitis

Chronic pancreatitis is an inflammatory disease of the pancreas, characterized by fibrosis and irreversible morphological changes, which may cause persistent pain, low quality of life, and permanent endocrine–exocrine function, as well as an increased risk for pancreatic cancer [4, 5].

Patients with chronic pancreatitis can be classified with TIGAR-O system into one of the six etiological categories: toxic (T), idiopathic (I), genetic (G), autoimmune (A), recurrent acute and severe pancreatitis (R), and obstructive cause (O) [6].

One of the key goals of chronic pancreatitis treatment is to relieve pain as it is the dominant symptom and its severity is significantly correlated with poor quality of life. According to current management strategies, surgery is not a prior approach, but a step-by-step approach is recommended, primarily using conservative treatment (using antioxidants, analgesics, pancreatic enzyme supplements, etc.), lifestyle changes (avoiding alcohol and fatty meals, regular sports), and endoscopy [7, 8]. When these methods fail, surgery is considered as a treatment option and its certain indications consist of recalcitrant pain and complications (common bile duct obstruction, pancreatic ascites, pseudocysts, duodenal or colonic obstruction, pancreatic fistula, and pancreatic cancer [10]).

Besides reducing the pain, endoscopic interventions are frequently used especially in pancreatic and/or biliary obstructions and chronic pancreatitis-related complications (e.g., pseudocyst) [9]. However, studies have shown that surgery (drainage or resection) has better results

compared to endotherapy in terms of pain control, and eventually 40–75% of patients will need surgery due to chronic pancreatitis-related pain [11, 12].

The ultimate goal of surgery should be to relieve calcitrant pain, improve patients' quality of life, maintain endocrine and exocrine pancreatic functions as much as possible, and prevent further hypersensitization and damage to structures surrounding the pancreas [14].

It is considered that increased fibrosis due to recurrent endoscopic interventions or the progression of the disease decreases the recycling of pancreatic functions and the success rate of surgery [13]. In this context, early/prophylactic surgery has shown to be superior in pain relief, preserving the exocrine–endocrine functions, and enhancing quality of life when compared to late surgery [18, 19, 29]. Animal studies have also shown clear benefits of early surgery [20, 21].

In their study of 297 cases, [28] reported that early surgery achieved complete or partial pain relief, reduced incidence of exocrine insufficiency and endocrine insufficiency, higher rate of resolution of both exocrine and endocrine insufficiency a better quality of life than later surgery group. It has also been shown that the etiology of chronic pancreatitis and postoperative complication rates do not affect early or late surgical outcomes. In another study, early surgery has been shown to reduce the rates of pancreatic insufficiency and provide better control of pain as well as low re-intervention rates [28].

Which surgical procedure will be performed is up to the radiological findings and the surgeon's preference. Among the surgical interventions, drainage (including Puestow procedure), resection (including Whipple procedure and pylorus-preserving PD, DP, and TP), or drainage plus resection (including Frey and Beger procedures) may be opted [15]. The standard approach is open surgery; however, laparoscopic or robotic interventions have been also applied in recent years [16, 17].

When the effect of surgical procedures on the success rate was compared, although there was no difference in terms of pain relief between the patient groups who underwent solely drainage and solely resection, the group that underwent drainage and resection (Frey and Berne procedures) had better results [30–32]. reported that PD had similar results with duodenum-preserving pancreatic resection (Beger's or Frey procedures) in terms of morbidity, mortality and quality of life, and shorter hospitalization and less blood loss [31].

10.4.3 Pancreatic Trauma

Pancreatic traumas are rarely encountered and constitute less than 1% of all traumas and 3.7–11% of abdominal traumas. Pancreatic trauma occurs most commonly after traffic accidents and blunt traumas. Although initial diagnosis is made with E-FAST in emergencies, CT is the most important diagnostic and follow-up tool in stable patients. In terms of treatment, the patient's stability after trauma is one of the most significant determining factors. According to guidelines prepared by The World Society of Emergency Surgery (WSES) and the American Association for the Surgery for Trauma (AAST), nonoperative management (NOM) should be considered primarily in hemodynamically stable patients. The patients, whose general condition has deteriorated while being followed, should also be prepared for exploration. In stable patients, the success of NOM increases with endoscopic and percutaneous interventional procedures for abscess, fistula, hematoma, or similar. CT should be repeated within 12–24 h, and the dimensions of the damaged area should be checked in order to determine whether surgical intervention is needed. It should be kept in mind that duodenum, liver, biliary tract, spleen, and vascular injuries may accompany in these cases rather than isolated pancreatic injury. Drainage is sufficient in cases with pancreatic trauma of WSES class I (AAST grade II). Radical resections are not recommended. Distal pancreatectomy can be performed in WSES class II (AAST grade III) cases. In the presence of a splenic trauma, splenectomy is also added to the procedure. Whipple procedure can be applied in destructive injuries involving the duodenum and the head of the pan-

creas (WSES class III, AAST IV-V). In cases of WSES class II-III (AAST grade IV-V), where the biliary tract is damaged, distal ducts should be ligated, and cholecystectomy and hepaticojejunostomy should be performed [79].

10.5 Miscellaneous Procedures

10.5.1 Portal Vein Resection

There is controversy about what to do in the presence of invasion from extrahepatic bile duct tumors into the portal vein. Some studies have reported that portal vein invasion is a criterion of inoperability, and resection does not improve survival. Kondo et al. (2008) reported that because bile duct tumors are very aggressive, resection should be performed for curative purposes at the first opportunity, and portal vein involvement is not considered as an inoperability criterion. Portal vein resection partially increases morbidity but also increases the chance of survival [80]. In cases with portal vein resection in short segments, end-to-end vascular anastomosis can be performed, while continuity can be achieved by using synthetic or vascular grafts (Fig. 10.2). Synthetic grafts have a high risk of occlusion, and vascular autografts (renal vein, saphenous vein grafts, etc.) should be preferred in appropriate cases. Marsoner et al. (2016) reported that they performed portal vein resection in 47 patients in a series of 221 cases operated for advanced pancreatic tumors, and it would be appropriate to perform it in selected cases [81]. Ebata et al. (2003) also argued that portal vein invasion has a negative effect on survival. However, more prolonged survival can be achieved with hepatectomy and portal vein resection [82]. However, there are also studies reporting that the addition of portal vein resection increases the risk of mortality and does not change survival [75, 80, 83].

10.5.2 Falciform Ligament Flooring

Post-pancreatectomy hemorrhage is one of the deadliest complications after pancreatic surgery and has been reported with an incidence of 5–16% in the literature. Hemorrhage may develop during the early period due to technical problems or fatal bleeding in the late period following pancreatic fistula and infections [84, 85]. Falciform ligament flooring is performed by laying the pedicula in front of the retroperitoneal zone vessels and fixing it. The anastomosis of pancreaticojejunostomy is expected to function as a protective shield between retroperitoneal vessels. In their series of 500 cases of pancreaticoduodenectomy, Okada et al. (2020) reported that bleeding was encountered less commonly in the falciform ligament flooring group (1.6%) than the group in which flooring was not performed (5.2%) [85]. However, discussions have been ongoing about its effectiveness in the literature.

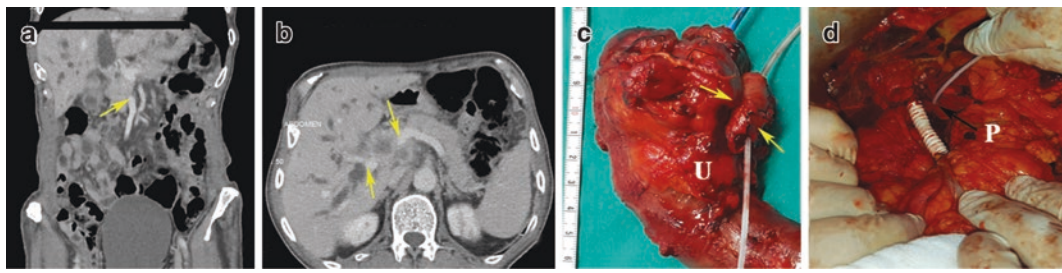

Fig. 10.2 Abdominal CT sections show portal vein invasion (yellow arrows) with uncinate tumor (**a**, **b**), and (**d**) shows the anastomosis of our patient using PTFE synthetic graft after portal vein resection (**c**). U uncinate process, P pancreatic duct

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11 Prophylactic Surgery for Gallbladder and Biliary Tract Pathologies

Osman Nuri Dilek and Nihan Acar

11.1 Introduction

Gallstones are a common health problem and have been diagnosed since the ancient world. Today, 20% of the population encounters a biliary tract pathology at some point in their life. Depending on the age of the patients, gallstones are detected in 10–33% of the population. Data on the natural course of gallstones are still controversial [1]. Although 140 years have passed since Langenbuch's first recipe for cholecystectomy in 1882, there was not much change in surgical technique. However, biliary tract surgery has reached very different dimensions owing to the great advances in laparoscopic, endoscopic, radiological, and minimally invasive procedures with ultrasonography, tomography, and magnetic resonance imaging techniques. As a result of advances in diagnostic tools, many biliary tract pathologies are detected earlier. On the other hand, biliary tract traumas have become more common than ever before as a result of increasing initiatives with the contribution of developing technologies. New horizons have been opened in hepatobiliary surgery with three-dimensional imaging, navigation techniques, robotic surgery, and hybrid operating theaters. With the advances in embolization, stenting, and drainage techniques, more comprehensive and more tissue/organ protective procedures have been started [2].

Prophylactic surgery of the gallbladder and biliary tract aims to eliminate life-threatening risks that impair quality of life. Since there are still many controversial issues in terms of indications, it is vital to follow actual literature and guidelines. In this chapter, indications, expected benefits, and possible harms of prophylactic surgical interventions of the gallbladder and biliary tract are going to be consecutively explained.

11.2 Gallbladder

Gallstones have an increasing prevalence worldwide, which has been reported between 10 and 33% [1, 3]. Fortunately, 40–60% of patients with gallstones have silent gallstones that do not cause any symptoms. While the others have complaints in the form of dyspepsia and biliary colic, and 20% of cases develop gallstone-related complications. Although we, surgeons, are quite familiar with the gallbladder disorders and their management, approach to asymptomatic gallstones has been still controversial. Since only 20% and sometimes fewer gallstones become symptomatic during the lifetime, prophylactic

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cholecystectomy (PC) is not recommended for every individual except for several instances [4–6]. Besides, approximately half of the patients with uncomplicated gallstones were found to have cholecystectomy surgery in the future due to persistent pain or complicated disease [7].

Cholecystectomy is one of the most common abdominal surgeries. Prophylactic cholecystectomy (PC) can be defined as the removal of the gallbladder without any further action. Incidental cholecystectomy (additional, concurrent, simultaneous) can be defined as adding a cholecystectomy to the procedure while performing another surgery. Indications and risks should be determined in patients with PC. Morbidity and mortality are undesirable. It is performed in the future to prevent cholelithiasis, acute cholecystitis and its complications, and second surgery.

It is essential to understand the etiology and risk factors of the gallbladder disorders leading to inflammation or malignancy to interpret better and introduce the indications for PC. Therefore, PC should aim to avoid several probable risks: a predisposition for severe acute/chronic inflammation, predisposition for cancer, hosting bacterial agents (such as *Salmonella Typhii*), and a secondary future intervention in patients who already have a high risk for surgery.

11.2.1 Asymptomatic Gallstones

Prophylactic cholecystectomy in asymptomatic cholelithiasis has long been a subject of debate. In the 1991 consensus meeting held in France, PCs under asymptomatic gall stones under elective conditions were not accepted [8]. However, in persons undergoing laparotomy for other reasons, performing simultaneous cholecystectomy is more accepted, but controversy continues. The main reason for the controversy is the emergence of cholecystectomy-related morbidities [9–12].

Female gender is a risk factor for stone production (the female-to-male ratio is about 4:1 during the reproductive years) and as well as conversion to the symptomatic disease [5]. Sood et al. (2015) reported the rates of symptomatic conversion as 5.36% and 16.83% in males and females, respectively [13]. Therefore, males can be managed expectantly, while PC should be considered in females with asymptomatic gallstones.

Ethnicity is also a determinative for deciding PC, since some populations have a significantly higher risk for both gallstone and cancer development. Those with gallstones have an increased risk of developing cancer 4–5 times [14]. North American Indians, the aboriginal populations of South America, and native Mapuche Indians of Chile have the highest risks for gallstone production worldwide [15]. In terms of gallbladder cancer, females from Delhi (India), South Karachi (Pakistan), and Quito (Ecuador) were reported to have a higher incidence [16, 17]. PC will be a reasonable choice in the aforementioned populations, and even the stones stay asymptomatic.

Metabolic syndrome, ***diabetes mellitus,*** and ***obesity*** are associated with the increased risk for gallstone development [15, 18]. Some authors, in addition, reported that diabetic patients were more likely to develop complicated disease [14, 19]. However, there are also studies supporting that PC for asymptomatic gallstones does not provide any significant benefits in diabetic patients but may in fact cause morbidity [20]. Therefore diabetes, alone, is not an adequate factor to recommend PC.

The size of the stones, which is the most considered and known factor, affects the decision of PC. Both large and small size carry a particular risk. Stones larger than 3 cm are associated with gallbladder cancer, while stones smaller than 3 mm with a patent cystic duct may be considered as a risk factor for symptomatic disease and biliopancreatic inflammation [21–23]. Besides, microlithiasis is also associated with metaplastic and dysplastic lesions which may arise from an undesirable, prolonged, and diffuse impact on the gallbladder epithelium [24]. In their prospective study of 592 cases with asymptomatic and symptomatic gallstones and gallbladder carcinoma, Csendes et al. (2000) presented that gallbladder carcinoma cases had significantly larger stones, regardless of the number of stones [25]. In addition, they showed that the patients with single stone were more likely to remain asymptomatic. These results which lead to the deduction of these

patients may not require a PC. Irrespective from the size of the stone, presence of a concomitant polyp always requires PC [14]. On the contrary, Choi et al. (2010) suggested that concurrent gallstones and polyps are not solely adequate to perform PC, and the criteria such as a thickened gallbladder wall and interval increase in the size of the polyps should be sought to determine the candidates for PC [26]. In their study of 180 patients from Karachi, Alvi et al. (2011) reported that stone size larger than 1 cm and solitary stone are the risk factors for developing gallbladder cancer [27]. Consequently, using a generalized cutoff value for the stone size in decision-making is inconvenient since each patient should be assessed with their own risk factors.

Choledocholithiasis, which is mostly related to gallbladder stones, can cause jaundice, cholangitis, and/or pancreatitis. Choledocholithiasis accompanies 10%–20% of the patients with symptomatic gallstones [28]. Endoscopic ultrasound and endoscopic retrograde cholangiopancreatography (ERCP) both have successful outcomes in terms of diagnosis and treatment of choledocholithiasis. Most common approach after the removal of bile duct stones is subsequent cholecystectomy since there is always a risk of recurrence as long as the gallbladder stays there [29, 30]. However, this cannot be accepted as a standard approach, since a contrary opinion has emerged in recent years proposing a wait-and-see approach after a successful ERCP [31, 32]. Schreurs et al. (2004) reported the rate of recurrent biliary symptoms after ERCP as 16% in patients with gallbladder in situ which was alike the normal population with silent stones [32]. Yasui et al. (2012) stratified this issue according to the patient age and concluded that it may not be necessary to recommend PC after endoscopic sphincterotomy in very elderly patients, since there was no significant difference between cholecystectomized patients and patients with gallbladder in situ, regarding the incidence of overall biliary complications among the patients older than 80 years [33]. On the other hand, developing a symptomatic choledocholithiasis in the presence of silent gallbladder stones can be interpreted as a conversion to symptomatic disease, and it is reasonable to act in this regard while making a treatment decision.

Medical history of ***pancreatitis*** is an important indication for PC. However, timing of the surgery and the approach in non-biliary pancreatitis have been controversial. Deciding when to operate patients with biliary pancreatitis has not always been as easy as deciding PC. The risk of developing cholecystitis or cholangitis increases after the first episode of biliary pancreatitis and may be encountered in up to 30% of those patients [34]. Uhl et al. (1999) evaluated the cases according to the severity of the pancreatitis. Therefore, they recommended PC after the symptoms relieved and laboratory tests normalized in mild pancreatitis, while in severe and necrotizing pancreatitis PC was recommended to be delayed until active inflammation subsided and fluid collections resolved [35]. There are also studies in the literature suggesting that even patients with idiopathic acute pancreatitis benefit from PC in terms of preventing recurrence [36, 37]. Since microlithiasis cannot be excluded in these patients, PC can be considered in medically fit cases.

11.2.2 Hematologic Disorders

Hereditary spherocytosis, ***sickle cell anemia,*** and ***thalassemia*** are the hemolytic anemias that tend to produce gallstones due to increased bilirubin metabolism. European Association for the Study of the Liver (EASL) in 2016 and Working Study Group on Red Cells and Iron of the European Hematology Association (EHA) in 2017 recommended simultaneous PC in cases undergoing splenectomy and having asymptomatic gallstones [38, 39].

Morbidity rate related with sickle cell disease after PC was reported between 4 and 7% [40, 41]. Therefore, PC can be considered in these patients in order to avoid a catastrophe that may be caused by the difficulties in differentiating an abdominal pain whether caused by a veno-occlusive incident or acute cholecystitis. However, routine PC in absence of gallstones is not recommended since the risk for developing gallstones is eliminated with splenectomy [42].

In terms of thalassemia, although routine PC is not recommended for silent gallstones, there are also authors advocating that PC under elective conditions should be considered also in asymptomatic cases due to the higher perioperative complication rate in these subjects, since most of them have to undergo surgery following at least one episode of cholecystitis [43].

11.2.3 Total Parenteral Nutrition

Parenteral nutrition is known to increase the risk of gallstones, and prolonged parenteral nutrition has the morbidity rate (associated with biliary complications) of 57% [44]. Therefore, PC can be performed during the index abdominal surgery in suitable patients, if gallstones are detected and prolonged parenteral nutrition is anticipated.

11.2.4 Short-Bowel Syndrome

Short-bowel syndrome is another issue which is quite related with parenteral nutrition. The factors, such as the remnant intestine shorter than 120 cm, dependency on total parenteral nutrition and the absence of terminal ileum increase the risk for gallstones [45]. The incidence of gallstones in patients with type III intestinal failure (chronic intestinal failure requiring long-term nutritional support) was reported as 21%, 38%, and 47% after 10, 20, and 30 years of observation, respectively [46]. However, there is no available data supporting PC in cases without gallstones. As it is recommended in parenteral nutrition, concomitant cholecystectomy during the abdominal surgery (resection or reconstruction) can be considered in these patients by evaluating the stability and life expectancy.

11.2.5 Drugs

Somatostatin analogs which are widely used in the treatment of neuroendocrine tumors have an unpleasant effect inducing gallstone formation [47]. Since symptomatic gallbladder disease that may develop during the treatment will cause disruption of the treatment, simultaneous cholecystectomy can be performed in cases for whom abdominal surgery is planned [47, 48].

There are ***various drugs*** commonly blamed for causing gallbladder disease such as ceftriaxone, erythromycin, ampicillin, cyclosporin, dapsone, anticoagulant treatment, and narcotic and anticholinergic medication [49]. However, there is not any prospective randomized trial or guideline to support PC in case of chronic exposure to these substances. Hence, utilization of any of these drugs should be a guide in decision-making in the presence of other factors leading to PC.

Another risk is ***chemical cholecystitis*** which occurs histologically in almost 100% of the patients who receive ***hepatic artery infusion*** [50]. This adverse effect is mostly encountered following the administration of mitomycin C and floxuridine/5-fluorouracil. Although various publications from late 1980s recommended PC in these cases at the time of pump implantation [50, 51], Carrasco et al. (1983) did not favor this opinion since the incidence of symptomatic disease was only 0.6% [52].

11.2.6 Transplantation

Transplant patients constitute a special group in terms of managing asymptomatic gallstones. These patients are as vulnerable to undergo a surgery as they are at risk because of immunosuppressive therapy which may mask any abdominal inflammatory condition. Graham et al. (1995) recommended pretransplant PC for all transplant candidates, since they had a high incidence of acute biliary complications, and urgent biliary surgery had significant morbidity and mortality due to immunosuppression [53]. On the other hand, Kao et al. (2005) disagreed with this opinion and they concluded that PC cannot be routinely recommended in all transplant patients with the current data [54].

Kilic et al. (2013) reported a series of 1687 cases who underwent heart transplantation

and cholecystectomy, and they strongly recommended performing cholecystectomy after transplantation in asymptomatic and uncomplicated gallstone patients due to the high risk of complications [55]. On the other hand, expectant management (wait-and-see) was recommended for pancreas and/or kidney transplant recipients with asymptomatic cholelithiasis by them [55]. Jackson et al. (2005) also showed that morbidity associated with gallstones did not increase after renal transplantation [56]. On the contrary, Moray et al. (2003) recommended to consider PC, with the concern of encountering complicated disease during the immunosuppressive treatment, for all end-stage renal disease patients with gallstones who are candidates for renal transplantation [57]. Cholecystectomy can be performed safely both in recipients and candidates [57, 58].

11.2.7 Bariatric Surgery

Higher body mass index (BMI) is associated with the higher risk for developing gallstones. Among the cases undergoing bariatric surgery, incidence of preoperative gallstones is 14–21%. In addition, rapid weight loss is another risk for gallstone formation which occurs in 22–71% of the cases after bariatric surgery [59]. Also, decreased cholecystokinin level after bypass procedures may lead to gallbladder hypokinesia, bile stasis, and eventually stone formation [60]. The incidence of symptomatic gallstones after bariatric surgery varies between 3.3 and 6.2% [61, 62].

Prophylactic cholecystectomy in bariatric surgery population is controversial in terms of its necessity and timing. The type of the bariatric procedure also affects the approach. For example, the future chance to undergo ERCP if needed remains in sleeve gastrectomy ± bipartition cases, while Roux-en-Y gastric bypass, mini-gastric bypass, and duodenal switch cases lose this chance. Morais et al. (2016) reported that only 3.3% of the 653 patients with intact gallbladder developed symptomatic gallstones and they did not recommend a routine PC in patients undergoing bariatric surgery [62]. In terms of sleeve gastrectomy, Raziel et al. (2015) showed that 9% of patients with asymptomatic sludge or stones required cholecystectomy after bariatric surgery due to developing symptomatic disease during the first postoperative year [63].

In their study comparing obese patients who underwent bariatric surgery (*n*: 2317) and were observed without surgery (*n*: 2331), Chen et al. (2019) did not find any difference in terms of the prevalence of gallstone disease and showed female gender and restrictive procedures as only risk factors for developing gallstone disease after bariatric surgery [64]. In contrast, it was also reported that Roux-en-Y gastric bypass had higher incidence of cholecystectomy after the index operation compared to sleeve gastrectomy [61, 65].

Major concerns about simultaneous PC are the technical difficulties caused by visceral obesity and trocar placement, the challenges in the management of biliary complications in obese patients, the higher rates of early postoperative complications, in-hospital mortality, and a longer hospital stay of 0.4 days [66, 67]. On the other hand, it is also reported that simultaneous cholecystectomy adds only 15–29 min and does not cause any additional complications [59]. Prophylactic cholecystectomy can be performed 6 months after index bariatric surgery in patients who have asymptomatic gallstones detected preoperatively and 1 year after in patients who do not have gallstones preoperatively but detected on ultrasonographic examination in postoperative first year [68]. These conflicting results should lead surgeons not to confusion, instead to one certain inference: "Tailored approach." Tailoring should be made according to the patient's clinical features, preferred surgical technique, surgeon experience, and facilities of the center. Patients' individual risk factors should be assessed and the decision should be made as it is in nonobese population. Cholecystectomy can be quite arduous in patients with central-type obesity and high BMI, and we recommend performing it in anatomically appropriate cases. Incidental cholecystectomy may be more appropriate in patients with peripheral-type obesity or lower BMI.

11.2.8 Precursors for Gallbladder Cancer

Age, gender, and ethnicity are the most common unchangeable risk factors for gallbladder cancer. Besides these factors, there are several lesions of gallbladder which are closely related with cancer and have been the subject of many studies in the literature [69].

Gallbladder ***polyps*** are commonly asymptomatic and majority of them are detected incidentally. Size, number, and morphology of the polyps, the patient's age, and genetics are the most significant factors to decide PC. In the literature, the rate of cancer development from polyps has been reported as 0–27% [70]. The guideline for gallbladder polyps published by European Society of Gastrointestinal and Abdominal Radiology (ESGAR) in 2017 recommended PC when the size of polypoid lesion is 10 mm or greater, the size of polypoid lesion is between 6 and 9 mm but accompanied by a risk factor, or polyp size increases by ≥2 mm [71]. In asymptomatic cases without any gallstones, if patient has risk factors (age >50 years, history of primary sclerosing cholangitis, Indian ethnicity, sessile polyp, including focal gallbladder wall thickening >4 mm), PC is considerable according to the same guideline (Fig. 11.1). In terms of the number of polyps, despite solitary polyp was once attributed as an indicator for cancer, it is not accepted as a strong indication for PC in current studies [72, 73]. Therefore, solitary polyps should be evaluated with the other risk factors for deciding PC [69]. Extraintestinal polyps in Peutz-Jeghers syndrome are rarely found in gallbladder. Since, malignant transformation of extraintestinal polyps has not been reported in the literature, Peutz-Jeghers syndrome, itself, does not create a special risk and polyps in these cases should be managed as in routine [74].

Adenomyomas are hyperplastic non-neoplastic lesions developing from the gallbladder wall. Adenomyomas are the most common benign polypoid lesions after cholesterol polyps (25%). It is reported that it is mostly seen in women over 50 years old and with a frequency of 2.5–5% [75]. They are usually located in the fundus (Fig. 11.2). They may be developed in generalized (adenomyomatosis), annular, segmentary, and localized forms [70]. It is reported that segmental adenomyomatous lesions on the gallbladder wall may be confused with cancer by causing concentric narrowing (hourglass gallbladder). Although it is generally accepted that there is no risk of cancer, there are also studies claiming it to be precancerous. The latest version of National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Hepatobiliary Cancers accept adenomyomatosis as a potential risk for developing gallbladder cancer [76]. Surgery should also be planned in

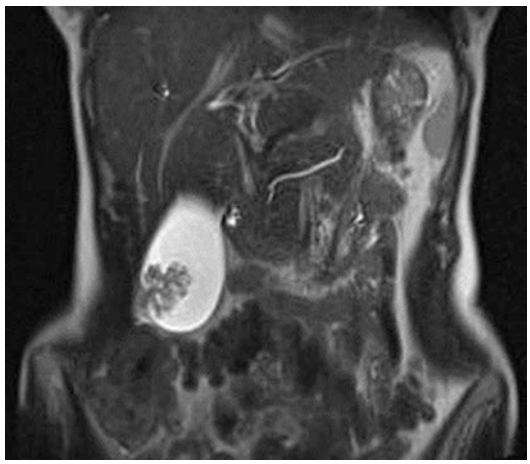

Fig. 11.1 The MRCP coronal section shows the polyp in the gallbladder

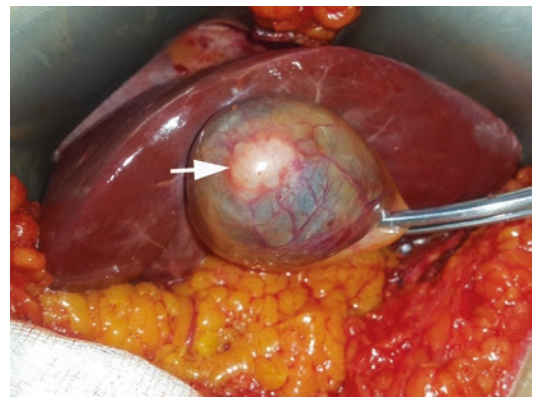

Fig. 11.2 An adenomyomatosis case originated from the gallbladder fundus

segmental adenomyomatosis cases, because they may be mistaken with cancer. The procedure to be performed in the treatment of the disease is laparoscopic cholecystectomy. Prophylactic cholecystectomy is recommended when the risk of malignancy continues. Due to the risk of cancer, the specimens should be removed by being put in an endobag. Open cholecystectomy should be preferred when cancer is suspected [70].

Our knowledge on the relation between ***porcelain gallbladder*** and gallbladder carcinoma is based on the studies from the first half of the twentieth century. In the literature, its incidence was given as 0.2%, and carcinoma was detected in 15% of porcelain gallbladders [77]. Towfigh et al. (2001) changed this infamous statement of porcelain gallbladder with their study of 10,741 gallbladders reporting that none of the porcelain gallbladders (0.14%) turned out to be carcinoma [78]. Therefore, cholecystectomy should not be routinely recommended in asymptomatic patients with porcelain gallbladders [79, 80].

Thickness of gallbladder wall should also be a warning in terms of gallbladder cancer. Seretis et al. (2014) reported an average gallbladder wall thickness of 4–5 mm in cases with gallbladder metaplasia [24]. Gallbladder wall thicker than 3 mm was shown as a risk for premalignant epithelial change in the gallbladder mucosa and so, PC should be considered in these cases [81].

Primary papillary hyperplasia (PPH) of the gallbladder is a rare precursor lesion for gallbladder cancer. Although PPH mostly lacks from invasive findings to the liver, it also demonstrates a vascular rich, solid tumor as it is in the cancer which makes the differential diagnosis quite challenging with preoperative diagnostic tests [82]. In order to obtain a definite diagnosis and to prevent a malignancy before developing, PC is recommended in PPH [73]. Frozen section may be useful to determine the extensiveness of the surgery.

Pancreaticobiliary maljunction is a rare congenital malformation of biliary tract, which has the incidences of 1:100,000 in Western populations and 1:1000 in Asian populations [83]. It defines the union of pancreatic and bile ducts outside the duodenum wall. This maljunction creates a predisposition to cancer by causing bile stasis and pancreatic reflux, which eventually result in histopathological changes in the epithelium of biliary system.

Bile duct dilatation, which may occur in 77% of the cases with pancreaticobiliary maljunction, is an important indicator to determine the risk for cancer and treatment option. The incidence of gallbladder cancer was reported as 13.4–21% and 37.4–77% in cases with and without biliary dilatation, respectively [84, 85]. The major challenge is to recognize pancreaticobiliary maljunction before malignant transformation in cases without biliary dilatation since these are usually asymptomatic. Takuma et al. (2012) proposed gallbladder wall thickness on ultrasonography as an indication for MRCP and EUS for suspected pancreaticobiliary maljunction without biliary dilatation [86].

Sole PC is usually adequate and recommended treatment option in cases with normal width bile duct [84, 87]. The approach in case of dilated bile duct is going to be explained in the prophylactic surgery for biliary tract pathologies.

11.2.9 Concomitant Surgery

Gastric cancer is one the most compelling issues in terms of management of asymptomatic gallbladder. Both the vagal cutdown and bypass of the duodenal passage have effect on the gallstone formation following gastrectomy. In the literature, the incidence of gallstone formation after gastrectomy was reported in a wide range 2.2–47 [88–92]. Fortunately, most cases appear to be asymptomatic, and only 0.5–5 of these cases reported to require subsequent cholecystectomy [88, 93, 94]. In order to better determine the indications for PC during the gastric cancer surgery, many other variables have been evaluated. Regarding the extent of gastrectomy, no difference was found between total and distal gastrectomy in terms of the incidence of gallstones [90, 91]. The extent of lymph node dissection is another point that needs attention. The removal or destruction of nerve system of gallbladder during the dissection around the hepato-

duodenal ligament disrupts gallbladder function which may result in gallstone formation. The incidence of gallstone formation was reported as 8.5–23% and 16.3%–42.1% after D1–2 and D3 dissections, respectively [90, 91]. Cholegas trial recruiting two groups (undergoing standard gastric surgery with or without PC), 130 patients with gastric cancer between 2008 and 2012, showed that nearly all biliary abnormalities found in the control group were sonographically detected after 4.5 years, the cumulative incidence of gallstones or biliary sludge increased in patients who were still alive in the fifth year of follow-up, and younger patients affected by symptomatic gallstones were at risk for the subsequent surgery. The authors of Cholegas trial concluded that concomitant PC during gastric cancer surgery was safe, although not effective for improving the natural course of patients and recommended to consider PC for younger patients with the early gastric cancer whose life expectancy is high [94]. In conclusion, although PC during gastric cancer surgery is not mandatory, it is a considerable option in cases undergoing extended lymph node dissection and with high life expectancy.

Esophagectomy also carries risk for gallstone formation with the same previously mentioned mechanism. Routine PC during ***esophageal cancer*** surgery was found to be safe but unnecessary, since gallstones occurred in 6.1% of the patients after esophagectomy and only 6.5% of these cases required cholecystectomy during follow-up [95]. Gillen et al. (2010) reported that late cholecystectomies can be performed safely and removal of a normal acalculous gallbladder during upper GI surgery cannot generally be recommended [96]. On the other hand, Miftode et al. (2014) advocated concomitant cholecystectomy based on the fact of increased surgical mortality in the cases of late cholecystectomy [97].

Ileal disease or ileal resection have been reported to be related with gallstone formation in ***Crohn's disease***. In their study of 8302 Crohn's disease patients with resected ileum, Goet et al. (2019) displayed that female sex, re-resection, and a later year of ileum resection were associated with the risk for future cholecystectomy [98]. In addition, PC in Crohn's disease was found to be associated with higher disease activity, lower quality of life, more hospital admissions, and higher risk for colonic dysplasia in the presence of diseased ileum [99]. Routine PC in Crohn's disease is not recommended due to possible undesirable effects, and when it is planned, individual risk factors should be introduced well.

Concomitant PC during surgery for ***colorectal cancer*** is also controversial. With the widespread utilization of the imaging tools for preoperative staging, colorectal cancer cases with gallstones have been encountered more frequently. Pezzolla et al. (1993), in their study of 23 patients who underwent concomitant cholecystectomy during colorectal cancer surgery and 23 patients who did not have gallstone, reported that postoperative complications and mortality were more frequent among the cases who underwent PC [100]. Some more recent studies showed that the rate of perioperative biliary complications (0.7%) and PC can be easily and safely performed during colorectal surgery [9]. Besides, gallstones were reported to increase general risk of colorectal cancer [101, 102] Therefore, PC during the index operation for colorectal cancer may also be considered as a preventive for future recurrence or metachronous colorectal cancer. However, actual data is not adequate to recommend a concomitant PC for colorectal cancer surgery.

On the other hand, this approach may be different in benign colorectal disorders such ***ulcerative colitis*** and ***ischemic colitis***. Cholecystitis may occur during or after ischemic colitis due to increased intra-abdominal pressure and/or splanchnic vasoconstriction. Moszkowicz et al. (2013) recommended PC in patients undergoing surgery due to ischemic colitis in order to prevent acute acalculous, with a low level of evidence [103]. They proposed this opinion, since a secondary operation may be catastrophic and challenging in unstable and fragile patients. However, operation time and surgical morbidity are also vital in these patients, especially the ones undergoing emergency surgery, so benefit and loss should be carefully evaluated when deciding PC. In terms of ulcerative colitis, unlike Crohn's disease, the risk for developing gallstones was not different than general population [104]. However, there have also been studies opposing

this inference. Ha et al. (2015) presented a prevalence of gallstone almost four times higher in patients with ulcerative colitis than normal population [105]. Risk factors for gallstone formation were indicated as elder age, multiple hospitalizations, hypertension, diabetes mellitus, and colectomy [106, 107]. These conflicting results require further investigation in order to determine the criteria for recommending PC in ulcerative colitis.

Simultaneous cholecystectomy of the asymptomatic gallbladder with curative resection of ***hepatocellular carcinoma*** in the left lateral section or Spiegel lobe resulted in higher postoperative complications. Consequently, the gallbladder should be preserved except in cases of gallbladder stones or polyps [108]. Besides, concomitant cholecystectomy is recommended in cases where right or common hepatic artery is ligated or embolized, in order to avoid gallbladder necrosis [109].

Cytoreductive surgery which aims to excise macroscopic disease by removing all the affected peritoneal surfaces and adjacent organs has been used widely in both primary and secondary malignancies (metastasis) of peritoneum [110]. As a part of omental bursectomy, cholecystectomy is also a component of cytoreductive surgery. In addition, PC may be required in cases who undergo diaphragmatic peritonectomy, excision of disease from the porta hepatis and liver's capsule [111].

In their study of 1257 cases who underwent ***open heart surgery*** due to coronary artery disease, valvular disease, and severe aortic stenosis, Charokopos et al. (2007) reported that they performed concomitant cholecystectomy in nine patients and concluded that these two procedures can be performed safely in selected patients at the same session [112]. However, all patients in that study had symptomatic disease.

11.2.10 Anatomical Variations

Anatomical variations of biliary system are seen in 7.3–47% of the population, and manifest as supernumerary structures, atypical shapes, atypical localization and/or atypical joint of ductal structures [113–116].

Multiple gallbladders are rare anatomical variations and divided into four subgroups according to which step organogenesis was affected. Their association with cancer is not clearly reported in the literature, so the indications for PC are vague. Type II multiple gallbladders were reported to have similar appearance with Todani type II bile cyst [117] Therefore, PC can be considered in these cases even if they are asymptomatic, since preoperative differential diagnosis is nearly impossible. Furthermore, supernumerary or the accurate number of the gallbladders is mostly discovered during the surgery which is being performed due to a symptomatic disease [118]. In this case, it should be emphasized that disease-free gallbladder(s) should also be removed to avoid any biliary complications.

Bilobed and hourglass-shaped gallbladders can also be encountered on preoperative imaging or during the surgery (Fig. 11.3).

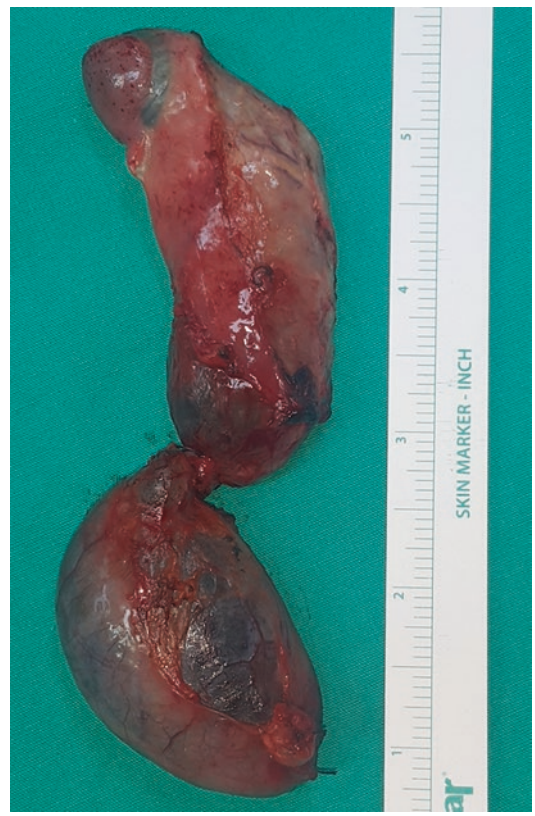

Fig. 11.3 An hourglass gallbladder that can mimic choledochal cysts is the specimen of our case

Since both entities are quite rare, PC for their asymptomatic onset is not well established. Nevertheless, the removal of the additional section during the index surgery should not be forgotten in order to avoid recurrence [119]. Hourglass shaped can be seen with adenomyomatosis of gallbladder, and PC is recommended due to the high cancer risk of adenomyomatosis [120].

11.2.11 Carrier for Bacterial Agents

Salmonella Typhi (S. Typhi) and *Salmonella Paratyphi A* (S. Paratyphi A) which are the bacterial agents of enteric fever can stay asymptomatic in gallbladder in 2–5% of the infected individuals [121]. These patients, which are defined as carriers, may not manifest any signs of disease, but still spread the bacteria by its fecal–oral route. Chronic carriage for S. Typhi is also related with gallbladder cancer due to chronic inflammation [122]. PC is a feasible approach when carriage for S. Typhi is confirmed in order to prevent both the spread of the infectious disease and the malignant transformation. However, it was also reported that cholecystectomy may not certainly eradicate the disease since the bacterial colonization can persist even in biliary tract, mesenteric lymph nodes, and liver [123].

11.3 Biliary Tract

Conditions of the biliary tract requiring prophylactic surgery are mostly related with the conditions requiring PC. Various preneoplastic pathologies may occur as a result of chronic inflammation and mucosal damage resulting from some congenital or acquired pathologies of the biliary tract. In this part, some preneoplastic and non-neoplastic conditions are going to be briefly re-mentioned as well as the conditions specific to biliary tract are going to be explained in detail.

11.3.1 Pancreaticobiliary Maljunction

Pancreaticobiliary maljunction leads to biliary duct cancer, with the previously mentioned mechanism, in 3.1–4% and 6.9–11% of the patients without and with biliary dilatation, respectively [84, 85]. Therefore, bile duct dilatation is the key point to determine the treatment approach. In cases with dilated bile duct, complete excision of the dilated extrahepatic bile ducts in addition to PC is recommended. Roux-en-Y hepaticojejunostomy or end-to-side hepaticoduodenostomy can be performed as the reconstructive techniques [124].

On the other hand, treatment approach in cases without biliary dilatation is controversial. Although majority of the studies have advocated that sole PC is adequate for the cases without biliary dilatation since bile duct cancer is not as frequent as gallbladder cancer, some studies have proposed an opposing opinion. Precancerous lesions, which were often not detected with preoperative imaging, were found in 73% of non-dilated bile duct cancers with pancreaticobiliary maljunction [125]. Additionally, recent studies showed that histological changes on the epithelium of non-dilated bile ducts were similar to dilated bile ducts [124, 126]. For these reasons, prophylactic excision of the extrahepatic bile duct is introduced as a reasonable approach by some experts regarding the prevention of carcinogenesis [87, 124]. However, prophylactic surgery for non-dilated bile duct in pancreaticobiliary maljunction should be evaluated carefully by considering the short- and long-term complications of biliary surgery.

11.3.2 Choledochal Cyst

Choledochal cyst is a rare congenital condition which usually manifests during childhood and rarely in adults. Its incidence was reported as 1:100,000–150,000 in Western populations and 1:1000 in Asian populations. Pancreaticobiliary

maljunction is responsible for 50%–80% of the cases [127]. Besides causing cholangitis and pancreatitis episodes, it also carries a risk of malignant transformation just like pancreaticobiliary maljunction. Previous studies have shown that 10–30% of adults with choledochal cysts develop cholangiocarcinoma, and choledochal cysts increase the risk for cholangiocarcinoma 20–30 times higher than general population [128]. A meta-analysis of 18 studies by ten Hove et al. (2018) showed that malignancies may develop in up to 11% of patients with choledochal malformation, and treating choledochal malformation may prevent developing malignancy. In addition, no differences in the prevalence of malignancy between the different types of choledochal malformation were found [129].

Treatment choices vary according to the classification introduced by Todani et al. (1977) [130]. Type I and type IV cysts have higher incidence for cancer, while type II and type III have a lower risk [128, 131]. 68% of cholangiocarcinoma are reported to be associated with type I cysts and 21% with type IV [132]. Therefore, less invasive techniques such as simple excision and endoscopic sphincterotomy are usually adequate for the treatment of type II and type III cysts, respectively, when the possibility of a concurrent cancer can be excluded.

Management of type IVA and V (Caroli's disease) cysts has been controversial due to the involvement of intrahepatic ducts. Cyst excision and an additional wide hilar hepaticoenterostomy can be performed in type IVA (Fig. 11.4). Cancer development is reported in 7–15% of patients with type V cysts (Caroli's disease) [132]. Hepatic lobectomy in localized type V cysts (Caroli's disease) can be preferred. However, since prophylactic liver transplant is not a feasible approach in asymptomatic cases, close surveillance for cancer development is recommended instead [133].

Despite all these preventive efforts, there is 1% risk of cancer development following the cyst excision [134]. Lifelong follow-up should be carried on in patients with choledochal cysts even after surgical interventions.

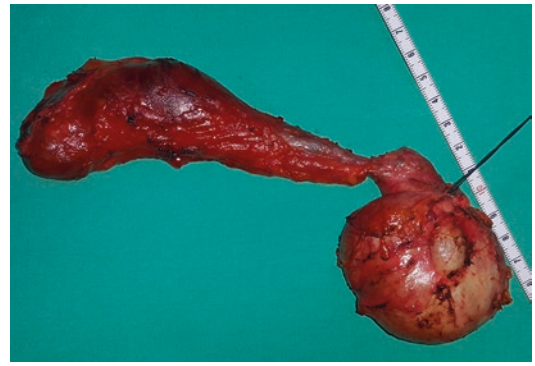

Fig. 11.4 This picture shows the specimen of a patient with a type 4 choledochal cyst

11.3.3 Biliary Intraepithelial Neoplasia (BilIN)

Biliary intraepithelial neoplasia (BilIN) develops as a result of chronic inflammatory processes such as primary sclerosing cholangitis (PSC), hepatolithiasis, choledoc cyst, chronic hepatitis B and C, and alcoholic cirrhosis. Patients with PSC have a high risk (>160 times) of developing cholangiocellular carcinoma. Cancer develops in 0.5–1.5% of patients with PSC each year, and the risk of developing lifelong cancer is calculated as 15–20% [135]. It was determined that BilIN developed in 10% of cases with hepatolithiasis. BilIN is a precursor lesion of cholangiocarcinoma and represents three different degrees of dysplastic changes of the epithelium. Although its prognosis is not clear, prophylactic surgical resection with PC should be performed when detected, in order to remove the risk of cholangiocarcinoma at an early stage. Detection of BilIN in surgical margins is an important problem in patients undergoing resection [132, 136].

Patients with Lynch syndrome have an increased risk of developing cholangiocarcinoma. Multiple primary papillomatosis is another

genetic disease, characterized by precancerous papillomatosis of the mucosa [132].

11.3.4 Intraductal Papillary Neoplasia of the Bile Duct (IPN-B)

Intraductal papillary neoplasia of the bile duct (IPN-B) is another rare entity that constitutes 10–15% of bile duct tumors [137]. It has three subtypes which are thought to be premalignant lesion of cholangiocarcinoma: adenoma, borderline tumor, and carcinoma in situ [87]. Complete surgical excision is the best treatment modality in cases without distant metastasis [138]. Surgical technique depends on the location of the tumor. Since the main goal is to achieve R0 resection, additional hepatectomy or pancreaticoduodenectomy should be considered in proximal and distant tumors, respectively.

11.3.5 Locally Invasive Gallbladder Cancer

Malignant cells in gallbladder cancer can spread through lymph vessels in the submucosal layer of the common bile duct, in addition to the large lymph vessels in subserosal layer [139]. With this concept, efficacy of the resection of extrahepatic bile duct in gallbladder cancer has been researched in many studies. In general, routine resection of the extrahepatic bile duct is not recommended in patients who have no involvement and have a negative cystic duct margin since major hepatic and biliary resections increase morbidity [140, 141]. Sakamoto et al. (2006) proposed resection of extrahepatic bile duct when perineural invasion exists, even in the absence of biliary infiltration [142]. Chikamoto et al. (2009), on the other hand, advocated en bloc resection of the extrahepatic bile duct in curative resection even for T2 gallbladder cancer due to the lymphatic spread through submucosal layer [139]. In several different studies, prophylactic extrahepatic bile duct resection in patients without macroscopic bile duct invasion has shown to have no survival impact [143, 144].

Laparoscopic cholecystectomy is the first treatment method in patients with cholelithiasis. However, in cases that are thought to have gallbladder carcinoma; it is recommended to perform surgery with laparotomy in terms of increased risk of port site metastasis (11–16%), gallbladder perforation risk (20%) and associated tumor spread, and presence of invasion and regional lymph tissue dissection [73, 145, 146]. Because of the risk of tumor, specimens should be removed in a special bag.

In 1% of cases undergoing laparoscopic cholecystectomy, gall bladder carcinoma is detected. In T1a cases, laparoscopic cholecystectomy is sufficient. The risk of vascular and perineural invasion increases in the lesions reaching the subserosis, and lymph node involvement is detected in approximately half of the cases [147]. In T1b cases, radical cholecystectomy should be performed. For this purpose, partial liver resection and port site resection should be performed, including a tissue 3 cm deep from the liver segments 4B and 5. On the contrary, NCCN does not recommend prophylactic port site resection, since it is not associated with improved survival or recurrence [76]. In T2 cases, segment 4B and 5 parts are included in the resection. From the cystic canal stump, sampling is done with frozen section. Extrahepatic biliary tract resection and regional lymph node dissection are also performed in cases with tumor-positive results [73].

Conditions that require liver resection and vascular resection in order to increase survival and success due to biliary tract tumors are described in the relevant section (See Chap. 9; Liver).

Prophylactic surgery of the gallbladder and biliary tract targets to eliminate various risks which eventually impair the quality of life. Since there are still many controversial issues in terms of indications, it is vital to follow actual literature and guidelines on this topic. Biliary tract operations should be performed in centers with high volumes, sufficient technical equipment, and experienced surgeons due to high morbidity and mortality risks.

11.3.6 Biliary Atresia

It is an idiopathic, progressive, fibrous obstructive neonatal disease of the biliary tract. The incidence is one in 10–20 thousand births. It is the most common cause of the yellowness of the newborn requiring surgical treatment. It may be accompanied by other organ anomalies and malrotations. In the etiology of the disease, viruses, toxins, genetic mutations (CFC1 gene, PKD1L1 gene), and immunological disorders have been blamed [148]. In patients generally diagnosed in the months after birth, bile drainage should be performed rapidly in order to prevent liver damage and cirrhotic process. Roux-en-Y type hepatoportoenterostomy (HPE) is the standard treatment method in the treatment of biliary atresia. HPE can be applied with laparoscopic and open surgery. However, complications such as fistula and stenosis developing in the early postoperative period are important causes of morbidity and mortality [149]. In studies conducted, it is recommended to perform HPE primarily in patients with biliary atresia, since the preprophylactic liver transplants to be performed in the early period cannot achieve the desired success due to technical difficulties (See Chap. 9; Liver). Following HPE cases, liver tissue is within normal limits in approximately one-third of the cases after 4 years. Approximately half of the cases require liver transplantation due to stenosis in the biliary tract or liver failure [150]. It is recommended that corrective restoration attempts in cases with stenosis are not successful, and liver transplantation should be performed due to the growth of children [148].

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Prophylactic Splenectomy

12

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12.1 Introduction

Splenectomy is performed for the palliative and radical treatment of primary splenic diseases, extrasplenic diseases, and splenomegaly. The first splenectomy was performed by Andirano Zaccarello in 1549 on a woman with massive splenomegaly. The first successful splenectomy for hematological disorder was performed by Quittenbaum in 1826 [1]. In 1893, Reigner reported the first successful splenectomy for splenic rupture [2]. Since the first report of laparoscopic splenectomy by Delaitre and Maignen in 1991, laparoscopic approach has become a standard procedure for elective splenectomy [3]. The first laparoscopic splenectomy in children was performed in 1993 by Tulman [4].

12.2 Splenectomy

Classically, splenectomy is performed for five main purposes: to stop bleeding, to extend the lifespan of the pathologic blood cells, in the treatment of the complications of splenomegaly, to remove the splenic masses and sources of diseases located in the spleen, and to establish the diagnosis. Indications for splenectomy can be divided into three groups: primary, secondary, and controversial (Table 12.1). The primary indications consist of the cases, in which there is no other alternative; splenectomy is the only effective treatment method. In secondary indications, splenectomy is an effective treatment method, but there are also other alternatives. In these cases, splenectomy should be selectively performed when other treatment methods are ineffective. Controversial group indicates the cases in which the effectiveness of splenectomy is not always high and splenectomy is considered as last resort.

The prophylactic splenectomy is to remove healthy or uncomplicated enlarged spleen to alleviate the clinical course of splenic and extrasplenic diseases and to prevent disease recurrence and complications of splenomegaly.

Indications for prophylactic splenectomy are not defined precisely and quite controversial. The splenectomy indications are as follows:

- Splenic echinococcosis.
- Gastric cancer.
- Cytoreductive surgery for ovarian cancer.
- HCC treatment.
- LDLT (living donor liver transplantation).
- Distal pancreatectomy.
- Chronic pancreatitis.
- Wandering spleen (mobile spleen).
- Splenic vein thrombosis (Banti syndrome).
- Hematological diseases.
- Sickle cell anemia.
- Splenic artery aneurysm.
- Cirrhosis.

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Table 12.1 Indications and contraindications for conventional splenectomy

Primary indications (splenectomy is the first choice)
• Severe splenic trauma (hemodynamic instability)[a]
• En bloc splenectomy in invasive tumors
• Primary tumors of the spleen[a]
• Injury of the pathological spleen
Secondary indications (splenectomy is not the only choice; it is proposed when other treatment options have no benefit)
• Splenomegaly and gastric varices due to splenic vein thrombosis
• Hereditary spherocytosis[a]
• Autoimmune hemolitic anemia
• Sickle cell anemia
• Idiopathic thrombocytopenic purpura (immune thrombocytopenia)
• Felty's syndrome (immune neutropenia)
• Splenic abscess
• Primary hypersplenism
• Pyruvate kinase deficiency
• Thrombotic thrombocytopenic purpura
Controversial indications (the benefit of splenectomy is controversial)
• Echinococcosis[a]
• Non-parasitic cysts[a]
• Thalassemia
• Lymphomas
• Myelofibrotic disorders
Contraindications
• Acute leukemia
• Agranulocytosis
• Asymptomatic hypersplenism
• Autoimmune lymphoproliferative syndrome (ALPS)
• Cold agglutinin disease
• Gaucher disease
• Hereditary stomatocytosis
• Hereditary xerocytosis
• Paroxysmal cold hemoglobinuria
• Thrombocytopenia in hepatic cirrhosis

[a]Indications may vary in part in advanced laparoscopy or interventional radiology centers

12.2.1 Splenectomy for Splenic Hydatidosis

Splenic hydatidosis is a rare disease and the next most common type of hydatidosis after liver and lung hydatidosis [5, 6]. It is reported that splenic hydatidosis occurs in less than 2% of abdominal echinococcosis and 0.5–8% of total echinococcosis cases [7].

Total splenectomy, partial splenectomy, spleen-preserving operations (pericystectomy, drainage of hydatid cyst), and PAIR are performed for the treatment of splenic hydatidosis. Total splenectomy is the most common operation for splenic hydatidosis, and it is considered as the radical treatment of the disease [6, 8, 9]. Splenectomy is demonstrated to decrease the defense against bacterial and parasitic infections and increase the incidence of pneumonia [10]. Parasitic infections, such as malaria and babesiosis, are increased in endemic areas [11–13].

There is no significant difference in recurrence between splenectomy and spleen-preserving surgery [14]. Also, it is reported that percutaneous treatment is a safe and effective method for splenic hydatid disease and may be the alternative treatment to surgery [15]. The possibility of the laparoscopic approach and spleen-preserving surgery is also noted in the literature [7, 14].

To sum up, it is difficult to realize which method is first-line treatment because current studies cover separate case series, and there are no randomized researches on comparative analysis of splenectomy and spleen-preserving surgery for splenic hydatidosis. Classically, splenectomy is proposed as a radical treatment of splenic hydatidosis, but it may cause susceptibility to bacterial and parasitic infection. Furthermore, spleen-preserving operations may increase recurrence risk. Although a few studies have been carried out, it is shown an increasing tendency in spleen-preserving surgery; in particular, laparoscopic and percutaneous interventions.

12.2.2 Splenectomy During Gastric Cancer Surgery

Attitude to splenectomy in gastric cancer surgery has changed over the last decades. Previously, splenectomy was recommended for the removal of the hilar lymph nodes at the splenic hilum in order to reduce the recurrence rate. However, randomized controlled trials demonstrated that in total gastrectomy for proximal gastric cancer which does not invade the greater curvature, prophylactic splenectomy

has no oncological benefit; on the contrary, it increases intraoperative bleeding and postoperative complications. Therefore, for gastric cancer which does not invade the greater curvature, splenectomy is not suggested [16, 17]. In recent years, it is reported that prophylactic splenectomy has no oncological benefit to patients with advanced proximal gastric cancer involving the greater curvature; on the contrary, it may increase complication rates [18, 19]. It is also demonstrated that removal of micrometastasis of lymph nodes at the hilum of the spleen and along the splenic artery has no impact on survival [20]. Also, in the literature, it is showed that splenectomy has no survival benefit for remnant gastric cancer [21].

Thus, if there is no splenic invasion of gastric cancer, prophylactic splenectomy is not recommended, regardless of the stage and the localization of cancer.

12.2.3 Splenectomy During Cytoreductive Surgery for Ovarian Cancer

Splenectomy may be performed during cytoreductive surgery for ovarian cancer. It is reported that survival of patients in whom splenectomy has been performed during cytoreductive surgery due to oncological indication is shorter compared with those who have not undergone splenectomy [22]. According to the results of this study, splenectomy during cytoreductive surgery for ovarian cancer remains in question.

12.2.4 Splenectomy for the Treatment of Hepatocellular Carcinoma

Splenectomy is not routinely performed in the surgical treatment of hepatocellular carcinoma (HCC). In the past few years, several studies note the benefit of simultaneous splenectomy during liver resection for HCC associated with cirrhosis. Cao et al. (2003) reported that splenectomy combined with hepatectomy for HCC associated with cirrhosis is helpful for the recovery of T-lymphocyte subsets and the maintenance of cytokine balance [23]. Sugimachi et al. (2008) suggest that patients with severe thrombocytopenia associated with HCC and cirrhosis may benefit from splenectomy combined with liver resection [24]. The clinical research performed by Zhang et al. (2015) indicates that hypersplenism has a negative impact on the outcome of HCC in patients with liver cirrhosis, and splenectomy increases disease-free survival. Therefore, the authors recommend performing synchronous liver resection and splenectomy in patients with HCC and hypersplenism [25, 26]. Another study reports the beneficial effect of partial splenic embolization in HCC [27].

To summarize, a few studies recommended splenectomy in patients with HCC associated with underlying cirrhosis in order to improve immune status and to increase disease-free survival. However more randomized studies are required for its routine utilization.

12.2.5 Splenectomy During Liver Transplantation

Classically, simultaneous splenectomy during living donor liver transplantation (LDLT) is performed to decrease portal pressure, prevent and treat small for size syndrome, and prevent antibody-mediated rejection in ABO-incompatible cases, in patients with splenic artery aneurysm, pancreatic tumors, large splenorenal shunts, and autoimmune hepatitis [28]. But in the literature, there are many incompatible results of prophylactic splenectomy during LDLT.

An experimental study has shown that splenic congestion promotes IL-2 excretion and macrophage infiltration within the liver and exacerbate hepatic ischemia-reperfusion injury. These results prove that splenectomy reduces hepatic ischemia-reperfusion injury [29].

Yoshizumi et al. (2017) have analyzed 306 patients who underwent LDLT. According to this study, prophylactic splenectomy decreases acute cellular rejection (13.2% vs. 23.5%) and increases the 6-month survival rate (94.8% vs.

86.2%) [30]. Similar results have been reported in other studies. On the contrary, Golse et al. (2017) report that splenectomy during LDLT increases portal vein thrombosis and infectious complication rates and should be performed in selected patients [31]. Furthermore, splenectomy during LDLT is not recommended according to another similar study. A meta-analysis of cohort and case-control study shows that simultaneous splenectomy during LDLT increases platelet count; decreases portal pressure, the incidence of small for size syndrome and rejection; increases operation time, intraoperative blood loss, the incidence of postoperative hemorrhage, thrombosis, and infection, but it does not improve survival. Therefore, the authors propose that splenectomy during LDLT should be performed in selected patients [28].

In conclusion, the problem of performing splenectomy during LDLT without typical indications has not been solved and randomized studies in this area are required.

12.2.6 Splenectomy During Distal Pancreatectomy

Splenectomy is sometimes performed during distal pancreatectomies because of its anatomical relation to the pancreas. But considering the physiological importance of spleen, spleen-preserving pancreatectomy is suggested for benign and low-grade malignant tumors. The results of two meta-analyses of spleen preservation versus splenectomy during distal pancreatectomy showed that spleen-preserving distal pancreatectomy leads to shorter operation time and hospital stay and decreased incidence of hemorrhage, pancreatic fistula, and infectious complications [32, 33]. According to the results of these researches, it is not proposed to perform splenectomy during distal pancreatectomy for benign and low-grade malignant tumors. There is not enough data on whether to perform splenectomy for malignant pancreatic tumors.

12.2.7 Prophylactic Splenectomy in Chronic Pancreatitis

Splenectomy is indicated in symptomatic forms of splenic vein thrombosis (SVT) caused by chronic pancreatitis (gastric fundal variceal bleeding, hypersplenism). Few studies have been conducted on the splenectomy in asymptomatic left-sided portal vein thrombosis [34, 35]. The results of these clinical trials note that complications of prophylactic splenectomy are less frequent than episodes of variceal bleeding due to SVT. For this reason, splenectomy is recommended during pancreatic resection in the presence of asymptomatic SVT.

12.2.8 Splenectomy for Wandering Spleen

Wandering spleen is a rare condition that may cause acute abdomen or presents as an asymptomatic abdominal mass. It mostly develops as a result of the ligamentous laxity or lack of ligaments. The spleen is not located in normal anatomic location, and pelvis is the most common localization [36]. Splenectomy is indicated for a twisted wandering spleen, and splenopexy and splenectomy are performed for an asymptomatic form to prevent the risk of complications (torsion, necrosis, acute abdomen, and trauma) [37].

12.2.9 Splenectomy in Hematological Diseases

There are mainly four reasons to perform a splenectomy for hematologic indications: (a) to remove the spleen without destroying diseased blood cells; (b) to prevent splenomegaly and hypersplenism; (c) Hodgkin's disease staging; (d) to clarify unclear splenomegaly with nondistinctive hematologic features [38].

Splenectomy is usually performed in patients with hematological diseases as a second-choice

treatment, and it is indicated for complications of splenomegaly or when medical treatment is not effective (Table 12.1). The benefits of prophylactic splenectomy in various hematological diseases are also reported.

Rezk et al. (2018) assessed prospectively the maternal and fetal outcome in women with idiopathic thrombocytopenic purpura (ITP) who have undergone earlier splenectomy compared to women on medical therapy [39]. The result of this study shows that higher rates of bleeding episodes, complications of steroid therapy, need for additional treatment of thrombocytopenia, defective lactation, preterm labor, and admission to neonatal intensive care unit were observed in patients in the medical group compared to patients in the splenectomy group. Due to the results, the authors recommend earlier splenectomy in patients with ITP wishing to get pregnant [39].

Sickle cell anemia can lead to complications with high mortality, such as acute splenic sequestration and splenic rupture. Splenectomy is an effective treatment of these cases. Gnassingbe et al. (2007) suggest splenectomy in children with splenomegaly for the prophylaxis of splenic rupture and acute splenic sequestration [40]. Splenectomy is recommended to perform in children over 5 years of age. In one of the studies, the outcomes of splenectomy performed in children under 5 years of age and over 5 years of age were analyzed. The study demonstrated that the incidence of complications after splenectomy is not higher in patients under 5 years of age compared with older ones. The authors stated the possibility of prophylactic splenectomy in children under 5 years of age and have experienced at least one life-threating crisis [41].

Prophylactic splenectomy is recommended as a treatment of hereditary spherocytosis. According to the model proposed by Marchetti et al. (1998), combined prophylactic splenectomy and cholecystectomy are of benefit to young patients with hereditary spherocytosis and gallstones [42].

In summary, prophylactic splenectomy may be performed in patients with various hematological diseases, especially in young women with ITP waiting to get pregnant, children with sickle cell anemia, young patients with hereditary spherocytosis, to prevent complications. But further randomized researches are needed.

12.3 Miscellaneous Conditions

12.3.1 Nonoperative Management of Splenic Trauma

Indications: Nonoperative management (NOM) of splenic injuries should only be considered for patients with hemodynamic stability and absence of other organ injuries requiring surgery and in an environment that provides capability for intensive monitoring, clinical evaluations, and an available operating room for urgent surgery.

Contraindications: NOM is contraindicated in presence of unresponsive hemodynamic instability and other indications to laparotomy (peritonitis, hollow organ injuries, bowel evisceration, impalement). Age above 55 years old alone, large hemoperitoneum alone, hypotension before resuscitation, Glasgow coma score <12 and low-hematocrit level at the admission, associated abdominal injuries, blush sign at CT scan, anticoagulation drugs, HIV disease, drug addiction, cirrhosis, and need for blood transfusions are not absolute contraindications for NOM, but they should be taken into account. If operating room for urgent surgery or angiography/angioembolization (AG/AE) is available, NOM could be considered in patients with The World Society of Emergency Surgery (WSES) class II–III spleen injuries with associated severe traumatic brain injury. If not, splenectomy should be performed.

Methods: Intravenous contrast-enhanced CT should be performed in patients being considered for NOM. AG/AE may be performed in hemodynamically stable and rapid responder patients with moderate and severe lesions and in those

with vascular injuries at CT scan (contrast blush, pseudo-aneurysms and arteriovenous fistula). AG/AE should be considered in all hemodynamically stable patients with WSES grade III lesions, regardless with the presence of CT blush. Hemodynamically stable patients with WSES grade II lesions without blush should not undergo routine AG/AE but may be considered for prophylactic proximal embolization in presence of risk factors for NOM failure. Angiography/angioembolization (AG/AE) could be considered in patients undergone to NOM, hemodynamically stable with signs of persistent hemorrhage regardless with the presence of CT blush once extra-splenic source of bleeding is excluded [43, 44].

12.3.2 Partial Splenectomy

Indications: Trauma (hemodynamic stability, no evidence of other intra-abdominal organ injury, no associated head injury, no coagulopathy, CT confirmation of isolated splenic injury), resection of nonparasitic cysts, hamartomas and other benign splenic tumors, inflammatory pseudotumor of the spleen, type 1 Gaucher's disease, cholesteryl ester storage disease, chronic myelogenous leukemia, thalassemia major, spherocytosis, staging of Hodgkin's disease in children.

Contraindications: Inadequate exposure, inability to mobilize the spleen and tail of pancreas to the midline, and inability to leave >25% of splenic mass for complete splenic function.

Methods: It has been shown in animal studies that preservation of 25% of the spleen allows an appropriate splenic function. If splenic regrowth occurs, completion splenectomy may be required. The technique of partial splenectomy includes ligation of the main splenic vessels and the short gastric vessels, preserving the pedicle arising from the left gastroepiploic vessels. Alternatively, ligation of the main splenic vessels and the preservation of the short gastric vessels can be performed. In both cases, about 10–30% of splenic parenchyma are preserved and a rim of devascularized tissue is left behind to reduce splenic bleeding [45].

12.3.3 Splenic Artery Aneurysm

Splenic artery aneurysm (SAA) constitutes more than 50% of all visceral aneurysms and is the third most common abdominal aneurysm after aortic and iliac artery aneurysms. Portal hypertension and pregnancy increase the risk of rupture, and ruptured aneurysm has a high mortality. Treatment is required for all symptomatic aneurysms and asymptomatic aneurysms larger than 2 cm in diameter and if the patient is pregnant or of childbearing potential. Surgical intervention is the treatment of choice. Ligation and excision are recommended for proximal aneurysms. Splenectomy is recommended to be performed during aneurysmectomy in distal (hilar) SAAs. Endovascular techniques (embolization, stenting) are used in patients who have a contraindication to surgery. Endovascular interventions have the risks of splenic infarction and recanalization of the aneurysm [46].

12.4 Conclusion

The prophylactic splenectomy is to remove undiseased or uncomplicated enlarged spleen for the purpose to alleviate the clinical course of splenic and extra-splenic diseases and to prevent disease recurrence and complications of splenomegaly. Classically, splenectomy is proposed as a radical treatment of splenic hydatidosis, but it is shown as an increasing tendency in spleen-preserving surgery, in particular, laparoscopic and percutaneous interventions. If there is no splenic invasion of gastric cancer, prophylactic splenectomy is not recommended, regardless of the stage and localization of gastric cancer. Splenectomy during cytoreductive surgery for ovarian cancer remains in question. Few studies note that splenectomy in patients with HCC associated with underlying cirrhosis improves immune status and increases disease-free survival; therefore, splenectomy is recommended by these authors. But more randomized studies are required. The problem of performing splenectomy during LDLT without typical indications has not been solved, and randomized studies in this area are required. It is not

proposed to perform splenectomy during distal pancreatectomy for benign and low-grade malignant tumors. There is not enough data on whether to perform splenectomy for malign pancreatic tumors. Splenectomy may be reasonable during pancreatic resection in the presence of asymptomatic splenic vein thrombosis. Splenectomy is an option for an asymptomatic form of wandering spleen to prevent complications (torsion, trauma). Prophylactic splenectomy may be performed in patients with various hematological diseases, especially in young women with ITP waiting to get pregnant, children with sickle cell anemia, young patients with hereditary spherocytosis, to prevent complications. But further randomized researches are needed. Splenectomy is recommended to perform during aneurysmectomy in distal (hilar) splenic artery aneurysm.

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Prophylactic Surgical Procedures for Esophageal Pathologies

13

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13.1 Introduction

The esophagus is defined as "the organ that God hides from surgeons," but it has become an organ open to all kinds of trauma or invasive intervention in parallel with today's biochemical and technological developments. The esophagus may require surgical intervention as a result of various traumatic and structural pathologies. The vast majority of esophagectomies are performed in the presence of cancer. Prophylactic esophagectomy and various prophylactic procedures are performed in selected cases today.

In this chapter, the place of prophylactic surgical procedures in esophageal pathologies including Barrett's esophagus, esophageal varices and its bleeding, corrosive esophagitis, achalasia, and some miscellaneous conditions are reviewed in the light of literature data.

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13.2 Barrett's Esophagus

Barrett's esophagus (BE) is a histopathological response that results in the transformation of the esophageal stratified squamous epithelium to columnar epithelium for many reasons. This change is defined as metaplasia, and subsequent dysplastic change is considered as the precursor of adenocarcinoma [1–3]. These changes are defined in five groups according to the Modified Vienna Criteria; Type 1: no dysplasia, Type 2: indefinite for dysplasia, Type 3: low-grade dysplasia (LGD), Type 4: high-grade dysplasia (HGD), Type 5: intramucosal carcinoma (IMC).

The factors in BE etiology are advanced age, male gender, white race, gastroesophageal reflux disease (GERD), presence of hiatal hernia, high body mass index, and central obesity. In addition, smoking, alcohol addiction, metabolic syndrome, sleep apnea, and type 2 diabetes mellitus may also be potential risk factors for the development of BE [1, 4, 5]. On the other hand, the presence of *Helicobacter pylori* infection reduces the risk of developing BE [6]. It is accepted that BE is existent in 1–2% of the European population and many patients are not aware of it. In the United States, its incidence is higher and 5.6%. The incidence is gradually increasing for the last five decades. During that period, the frequency of adenocarcinoma related to BE has increased from 10% to 50% today [6]. The lifelong risk of carcinoma development in individuals with BE was calculated as 5.6% in men and 3% in women

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[1]. BE is considered as a public health problem due to the risks it contains.

With the progression of pathological processes such as reflux, metaplastic changes may result in LGD, then HGD and IMC, and then advanced adenocarcinoma, respectively. However, it is difficult to predict the natural course of BE and may vary depending on genetic, environmental, and personal factors [1]. In the large LGD series of Sharma et al. (2020), 6/1000 of patients developed adenocarcinoma each year [3]. In the study of Rastogi et al. (2008), it was reported that the risk increased in the 5-year follow-up of patients with HGD, and adenocarcinoma developed in 6/100 patients each year [7]. On the other hand, although there is no definitive evidence, the risk of malignancy was reported to be five times higher in cases with BE accompanied by intestinal metaplasia in Western countries [1, 8]. Adenocarcinoma develops within 5 years in 10–59% of patients with BE developing HGD [9, 10]. The risk of malignancy increases 30–50 times in patients with BE [11]. In addition, individuals with BE were reported to develop adenocarcinoma at a rate of 21–95%, depending on the degree of dysplasia [12]. The risk is higher in the cases of BE with long segment (>3 cm) involvement [6]. It was reported that patients with HGD may develop cancer in a period of 0.75–9 years [13]. It is thought that if patients with HGD are followed, all of them will develop adenocarcinoma. Today, however, the incidence has decreased around 5.9–11.7% with the advanced protocols and increasing use of diagnostic tools such as high technology endoscopy systems and endoscopic ultrasound (EUS) [14].

In cases with non-dysplastic BE, the first step is to eliminate the cause of reflux [2, 3]. For this purpose, prophylactic anti-reflux surgeries have been used frequently, as well as changing lifestyle, diet, and medical treatment. Laparoscopic anti-reflux surgery has been one of the most commonly performed prophylactic procedures in the United States (See Chap. 15; Stomach-Benign). According to the long-term follow-up results of large series, medical treatment and anti-reflux surgery reduce the risk of cancer [15, 16]. In the literature, it was reported that dysplasia might regress after anti-reflux surgery in patients with BE and LGD, but it would be more difficult for Barrett's epithelium to regress. Although the issue is still controversial, the progression of the disease in patients undergoing ablation due to intestinal metaplasia and LGD is known to stop [1, 17, 18].

In recent years, depending on the improvement in endoscopic methods, endoscopic approaches have come to the fore in the diagnosis and treatment of BE. Many histopathological studies showed that it is not always possible to differentiate HGD with in situ carcinoma. Moss et al. (2010) detected a short segment (less than 3 cm) HGD in 89% and IMC in 11% of cases with endoscopic biopsy in their study conducted with 75 cases [19]. However, almost half of the results changed after the endoscopic resections, and they found that 4% of the cases had no dysplasia, 53% had HGD, 19% had LGD, 13% had IMC, and 9% had submucosal adenocarcinoma. According to the results of the same study, they achieved complete BE eradication in 94% of the patients who underwent 1–3 sessions of endoscopic mucosal resection (EMR) for endoscopic eradication and the number of prophylactic esophagectomies decreased dramatically. They performed prophylactic esophagectomy due to the depth of HGD and relapses in five cases [19]. In the 68 prophylactic esophagectomy performed by Nasr and Schoen (2011) due to HGD, they found that 12 cases had adenocarcinoma, 2 cases had actually LGD, and 54 cases had HGD [14]. EUS is a very decisive diagnostic tool in defining the depth of the mucosal lesion and grading dysplastic changes [20].

There are algorithms and recommendations developed by the American Gastroenterological Association (AGA) to accurately identify LGDs [2, 3]. Early diagnosis is possible with endoscopic follow-up and biopsy protocols (four-quadrant biopsies from every 1–2 cm area). Endoscopic surveillance programs have been started to be applied by AGA for endoscopic eradication of dysplasia developed in Barrett's epithelium. Accordingly, repeated EMR with periodic controls in patients with dysplasia is recommended and ablation (photodynamic

therapy, radiofrequency ablation, and argon plasma coagulation) for appropriate cases [1, 9, 21, 22]. EMR has been increasingly being used in the treatment of BE as a substitute for surgery in the last two decades [9]. Although endoscopic submucosal dissection (ESD) is another alternative option, it was reported that there is no difference in terms of complications, positive surgical margins, lymph node positivity, local recurrence, or metachronous lesions between two methods [23]. There are studies in the literature reporting that complete eradication can be achieved with EMR in patients with BE [2, 24, 25]. However, EMR can only be performed in suitable and selected patients. EMR is not recommended in patients with ulcers invading deeper layers than submucosa and in cases with suspected lymph node involvement [9, 26]. The biggest disadvantages of recurrent control endoscopies and recurrent EMR are the fibrosis and stenosis. The risk increases even more in large and long-segment lesions, relapses, and recurrent procedures [17, 18]. Eradication with endoscopic methods was recommended to be preferred first [22, 27]. In the same study, it was reported that 8–33% of cases with submucosal invasion may have lymph node involvement, and in these cases, EMR will be insufficient and therapeutic esophagectomy should be performed [22]. In a systematic review conducted with 2092 T1 case, 4% of the patients who underwent EMR or ESD had IGD, 14.6% HGD, 19% carcinoma in situ, 54% IMC, and 16% submucosal cancer [28].

Prophylactic esophagectomy refers to the resection of the esophagus in patients with BE who have HGD but have not developed adenocarcinoma. It includes patients who were not diagnosed with IMC or adenocarcinoma in the preoperative period. Procedures to be performed in patients with BE with adenocarcinoma should be for curative purposes. T1a and well-differentiated T1b adenocarcinoma foci smaller than 2 cm in diameter are recommended to be removed with ESD. In recent years, there are also studies suggesting esophagectomy instead of ESD in intramucosal poorly differentiated (T1a) or lesions larger than 2 cm in diameter [22, 29].

It should be noted that Barrett's epithelium adjacent to the squamous epithelium may be buried under the squamous epithelium. This condition, which is defined as Buried Barrett's esophagus, occurs in 28% of cases, and it is recommended to perform resection with a squamous epithelium of at least 1 cm during EMR or surgical resection [24]. In cases where the surgical margins are positive, esophagectomy and regional lymph node dissection should also be performed. In these cases, dissection of at least 15 lymph nodes is also recommended [29]. In the literature, the presence of LGD or HGD in the epithelium adjacent to the adenocarcinoma was detected in 50–91% of patients who underwent esophagectomy due to BE in the 1990s [30–32]. Adenocarcinoma was found in 13–75% of the patients who underwent prophylactic esophagectomy for HGD [9, 22, 30, 33].

In the 1990s, Hamilton and Smith [30] and Obertop et al. (1993) strongly recommended performing prophylactic esophagectomy in patients with HGD who had a low risk of surgery in the treatment of BE [32]. Although prophylactic esophagectomy was recommended to be performed through a transhiatal approach (Orringer technique) before, it has disadvantages such as the higher risk of lung complications and mortality. However, this method has the advantages of being able to provide safe proximal surgical margin negativity and allow performing cervical anastomosis to reduce the risk of anastomotic leak. When performing prophylactic transhiatal esophagectomy, it is recommended to remove the N1 lymph nodes, maintain the integrity of the muscle tissue, and avoid perforation [13, 16]. Prophylactic esophagectomy can also be performed using two-field-incision (Ivor-Lewis) or three-field-incision (McKeown) techniques. More lymph node dissection can be achieved with thoracotomy.

Markar and Hanna (2015) reported that minimally invasive esophagectomy should be preferred in terms of morbidity and mortality. They recommended performing prophylactic esophagectomy in cases where eradication cannot be achieved despite performing three or more EMRs. Minimally invasive esophagec-

tomy can be performed with a laparoscopic or thoracoscopic approach. With minimally invasive procedures, pulmonary complications can be reduced and quality of life can be improved [16, 34]. Vagal-sparing esophagectomy technique is also recommended to prevent dumping syndrome [35]. In this technique, right and left vagus nerves are isolated, highly selective vagotomy is performed, and esophagus is dissected with a vein stripper. The vagal-sparing esophagectomy, described by Akiyama from Japan, has advantages such as reducing the risk of dumping, protecting gastric drainage and gastric secretion, and reducing the risk of infection. This technique is mostly recommended for cases that require esophagectomy for benign disease because standard lymph node dissection is not performed. However, this method is not recommended in patients with BE with lymph node involvement [35, 36]. The inversion esophagectomy described by Hoppo et al. (2011) may be an alternative option [36, 37]. Mortality of prophylactic esophagectomy in various series was reported to be 1.7–10% and morbidity as 45%, which are the biggest disadvantages [3, 16, 22, 38]. It is suggested that prophylactic esophagectomy should be performed in experienced centers where more than 20 esophagectomies are performed annually, thus it is stated that mortality will be less than 5% [39]. Prophylactic esophagectomy can also be performed with laparoscopic and robotic surgery [16, 36].

The depth of the lesion and the presence of lymph node involvement should be evaluated in patients undergoing prophylactic esophagectomy. In patients with BE, a candidate for prophylactic esophagectomy, a detailed examination should be administered in terms of IMC, invasion depth of the lesion, and lymph node involvement. Prophylactic esophagectomy to be performed in patients with lymph node involvement will be insufficient and thus early recurrence and metastasis may be seen. Different results were found in the follow-up of patients who underwent prophylactic esophagectomy. It has been reported that cases with endoscopically HGD without IMC presence (T1a) will not metastasize to lymph nodes, but local submucosal invasion (T1b) may occur in 7% of the cases and accompanying lymphatic invasion may occur in 20–50% of these cases [9, 17]. While the incidence of IMC was high in the 1990s, it is much lower nowadays [22, 38]. Endoscopic follow-up and EUS should be the first step procedures for accurate diagnosis. Abdominal computed tomography (CT) can reveal adjacent and distant lymph node involvement. Positron emission tomography (PET)/CT can provide more accurate results about status of lymph node involvement [40]. In the prophylactic esophagectomy series of Tseng et al. (2003) with 60 patients, occult cancer was detected in 13 (43%) out of 30 patients with HGD in the first half of the study, and occult cancer was detected in 5 (16.7%) out of 30 patients who underwent surgery in the second half of the study. Some studies recommended performing prophylactic esophagectomy in selected appropriate cases and in experienced centers [13, 38]. Adenocarcinoma occurred in 16% of 75 cases as a result of the 7-year follow-up of patients in the prophylactic esophagectomy series of Schnell et al. (2001) [10]. Most of the cancer development occurred in the early postoperative period and in the first year. Due to undetectable IMC cases, endoscopic follow-up in the early postoperative period (1 year) of patients with prophylactic esophagectomy is recommended to perform more functional and aggressive.

As a result; today, complete eradication can be achieved in 87% to 96% of cases with endoscopic methods. Although prophylactic esophagectomy was considered as the first option in the treatment of patients with BE and HGD in the 1990s, its indications have gradually decreased in recent years [41]. Prophylactic esophagectomy may be recommended in treatment-resistant cases or when dysplastic changes cannot be eradicated despite anti-reflux surgeries, lifestyle changes and medical treatment, or LGD or HGD cases complicated with stenosis (6%), ulcer, and hemorrhage (1%) [3, 34, 35, 42]. Prophylactic esophagectomy should be performed in high-volume centers with experienced surgeons. Mucosal ablation protocols should be applied in patients who refuse surgical intervention.

13.3 Esophageal Varices

Esophageal varices are one of the most lethal complications of portal hypertension (PH). PH is that the pressure gradient in the portal vein is more than 6 mmHg due to pathological reasons. Varicose veins are seen in 7–8% of patients with compensated cirrhosis annually. Esophageal varices develop in 30% of compensated cases and 60% of decompensated cases [43, 44]. Every year, 10–11% of developing varicose veins turn into larger varicose structures (they contain red wale marks—similar to whip marks) and their bleeding potential is high. Bleeding of varicose veins is associated with the condition of the patient according to the Child-Pugh classification, and the diameter of the varices and whether there is a red wale mark on the varices [43, 45]. Hepatic venous pressure gradient (HVPG) is found above 10 mmHg in patients with PH and varicose veins. Although varicose veins have a mortality of 20% in 5-year follow-up, the mortality rate increases to 80% with other comorbidities. There are studies reporting that 15–50% of cases with first-time hemorrhage due to varicose veins die [46]. The risk is higher in decompensated cases. The risk is much higher in patients with HVPG above 20 mmHg or in patients with infection [45, 47, 48].

The first approach in patients with compensated cirrhosis and varicose veins is prophylaxis. For this purpose, the first step is to use a nonselective beta-blocker. Periodic follow-up of these patients is performed endoscopically. Endoscopic band ligation or sclerotherapy is applied for growing varicose veins. Complete obliteration can be achieved by applying prophylactic ligation at 1–2-week intervals. However, excessive and recurrent ligations can cause dysphagia, ulceration, hemorrhage, and strictures. The ligation process is not a therapeutic process, but a local treatment. If PH continues, ligation process does not prevent appearing new varices. The first approach in bleeding varicose veins is medical and endoscopic. However, it fails in 20% of cases. In such cases, the mortality risk is very high, bridge therapy should be planned, and balloon tamponade should be applied. Hemorrhage can be taken under control in 80% of cases via the balloon tamponade (Sengstaken-Blakemore tube) [49]. The mortality of the procedure is approximately 20% and it is the biggest disadvantage that it cannot be applied for more than 24 h due to its serious morbidity. Definitive operation after 48–72 h should be planned in patients undergoing balloon [44]. Recently, local self-expandible metal stents have become more preferred in treatment-resistant cases because of easier application and less morbidity. Side-to-side anastomosis is performed with the help of a suitable expandible wall stent with the transjugular intrahepatic portosystemic shunt (TIPS) method, which is a radiological interventional method. TIPS is considered an effective option in patients who cannot remain stable in the first 5 days with medical and endoscopic treatment. It is reported that hemostasis can be achieved in 90% of cases with TIPS. TIPS will also significantly reduce the amount of ascites in the patient [49–51].

Although obliteration of varicose veins with endoscopic methods decreases rebleeding, bleeding recurs in 60–70% of the cases within 2 years after the index bleeding [43, 48]. Each patient should be evaluated with a multimodal approach within their own conditions. There is consensus that the first therapeutic approach should be medical treatment and endoscopic intervention in recurrent bleeding [52]. In the 2007, Guideline of the American Association for the Study of Liver Diseases (AASLD) group recommended TIPS in patients who could not remain stable despite medical and endoscopic treatment [53]. It is reported that 59–77% of patients undergoing TIPS have stent stenosis or obstruction within 2 years [54, 55]. However, this rate decreased with the development of closed-cell stents [53, 56]. In the TIPS study conducted with 71 patients of Chen et al. (2019), after 1–24 months of follow-up, encephalopathy rate was found 12.1%, the recurrent bleeding rate was found 18.2% [53]. Additionally, it was reported that five patients died, four patients developed stent dysfunction, and success rate was found 93% in the same study.

Surgical options should be considered in patients whose bleeding cannot be stopped

despite medical, endoscopic, and radiological interventions. The significance of surgery in the treatment of PH has decreased considerably in the last two decades. Shunt surgeries and devascularization operations are performed in limited number of centers and selected cases [44]. Today, shunt surgeries and devascularization surgeries are performed in selected cases for emergency, therapeutic, or prophylactic purposes in order to decrease the portal pressure or decompress the varicose veins. Surgery may be required in cases of TIPS failure or dysfunction (stenosis, obstruction). The risk of mortality (30–50%) due to hypovolemia, malnutrition, and coagulopathies in patients undergoing emergency surgery is very high. In elective operations, mortality risk decreases to 15–30%. Liver transplantation is preferred in treatment, as a result of advances in transplantation surgery and increased standards after the development of end-stage liver failure, in liver patients who are successfully followed up with aggressive medical and endoscopic methods.

In shunt surgeries, decompression of portal blood flow (hepatopetal) with full, partial, or selective shunts is aimed (See Chap. 9; Liver). Nonselective shunt surgeries such as end-to-side or side-to-side portocaval shunts, mesocaval interposition, and central splenorenal shunt are effective in reducing portal blood pressure. In addition to preventing variceal bleeding, they provide a serious decrease in the formation of ascites. In addition to effectiveness in decreasing portal pressure, portosystemic shunts can also cause serious comorbidities. Metabolic problems such as hepatic encephalopathy and hepatic failure at different levels may occur as a result of portocaval decompression. In selective surgeries such as distal splenorenal shunt, liver functions are relatively better and metabolic complications are less common [51, 57, 58]. In a systematic review comparing patients with recurrent bleeding and underwent shunt surgeries or TIPS or endoscopic treatment, bleeding was more effectively prevented and mortality and encephalopathy were seen less common in patients who underwent portosystemic shunts compared to patients underwent TIPS or endoscopic treatment [59, 60].

Various procedures were described for devascularization of the esophagus. Some procedures are complicated techniques such as surgical devascularization, ligation, and transection of the esophagus with devascularization. In emergent cases, transgastric esophageal transection with staples can achieve optimal control of bleeding. Devascularization and mobilization should cover an esophageal segment of at least 7 cm from the gastroesophageal junction. This procedure can also be performed for prophylaxis. High selective vagotomy and devascularization of the stomach can be added to the procedure. Although various devascularization surgeries were described in the literature, devascularization of the esophagus, transection with stapler, and splenectomy procedure (Sugiura procedure) have become popular [23]. Lower risk of encephalopathy (<10%) observed after devascularization surgeries is an advantage of these procedures. Devascularization operations can also be preferred in cases with PH associated with portal vein thrombus.

In patients with varicose veins, emergent, elective, or prophylactic approaches are performed to prevent morbidity and mortality. Today, endoscopic methods can stop hemorrhage in most (>90%) cases. Nowadays, the primary preference in patients with end-stage liver failure is liver transplantation. In cases where bleeding cannot be stopped, in cases of dysfunctional TIPS, and in selected cases, urgent shunting or non-shunt interventions may be applied, while prophylactic in cases with high risk of bleeding or rebleeding.

Apart from the shunts, there are other options such as terminal esophagoproximal gastrectomies (TEPG), esophageal transections (ET), and Sugiura procedure to prevent esophageal variceal bleeding. These procedures can be applied for the therapeutic purpose as well as for prophylactic purpose [61]. The prognosis of patients underwent these surgeries was reported to be better compared to other patients [62]. Five-year survival was found to be 85.9% in patients with prophylactic TEPG and 81.6% in patients with ET [61]. Five-year survival of Child A patients was reported to be higher compared to Child B patients [63]. After 5 years, varicose veins recurrence was lower in

the TEPG group (18.4% vs. 26.4%) and 10-year survival was significantly lower in the TEPG group (59.3% vs. 70%) [61]. Although the recurrence of varicose veins in the TEPG group is lower during 10 years of follow-up, the reason for lower survival is that reflux esophagitis, bleeding, liver failure, and anastomosis ulcer development are two times higher [61].

13.4 Corrosive Esophagitis and Strictures

Corrosive substances are chemicals that can directly cause tissue damage upon contact. Some patients may be asymptomatic after corrosive substances ingestion (CSI). In some patients, increased saliva, loss of appetite, dysphagia, painful swallowing, burn marks on mouth and pharynx, retrosternal burning, abdominal pain, hematemesis, fever, vomiting, leukocytosis, tachycardia, agitation, and dyspnea [64]. Visceral perforation should be considered in cases such as persistent fever, peritonitis, chest pain, and hypotension. In this case, emergency surgery should be considered [65, 66].

The gold standard in determining tissue damage is esophagogastroduodenoscopy (EGD) [67]. Some authors stated that EGD administration is unnecessary in those who are asymptomatic after CSI [68, 69]. Bonavina et al. (2015) showed that CT is a better option than EGD in patient candidate for emergent surgery [70]. The superiority of EUS, a new imaging tool, to endoscopy has not been demonstrated [71].

Stricture can be seen in 32% to 75% of patients with a high degree of damage and applied long-term treatment [72]. Stricture formation is observed in 80% of patients within 8 weeks [66]. For stricture evaluation, barium esophagography and endoscopy can be used. Barium esophagography shows the size and formation of the stricture. Endoscopy detects mucosal recovery and the location of the stricture.

Endoluminal dilatation is the first step treatment method widely accepted in CSI-related stricture formation [67]. Today, many centers use balloon dilatation under radiographic control [67, 72, 73]. Balloon dilators have a lower risk of perforation than conventional bougie dilatation methods [67, 74]. Dilatation procedure should be started in 4–6 weeks after CSI [75]. The frequency of dilatation should be done first in every 1–3 weeks until oral intake is achieved. Then, as long as there are signs of stricture, the procedure should be repeated until swallowing is achieved [76, 77].

Adenocarcinoma or squamous cell carcinoma may develop in the esophagus after CSI-related stricture formation [65]. Endoscopic surveillance is recommended to start 15–20 years after CSI [78]. Control is suggested every 1–3 years thereafter [77, 79]. Studies have been conducted for the early diagnosis of esophageal squamous cell carcinoma in children with CSI-related esophageal stricture. For this purpose, esophageal microRNA expression profiles have been examined. It has been noted that miR-374 and miR-574 as potential biomarkers of early diagnosis of cancer can be the basis for validation of miRNAs [80].

Gastric outlet obstruction mostly occurs after concentrated acid ingestion [81]. Balloon dilation or surgical intervention may be required in case of gastric outlet obstruction. In treatment-resistant strictures, gastric tube esophagoplasty, colonic interposition, jejunal interposition, colonic patch esophagoplasty, or gastric advancement flap surgery may be required with partial esophageal resection [65].

13.5 Achalasia

Achalasia is a primary motility disorder with inadequate relaxation of the lower esophageal sphincter (LES). The absence of peristalsis results in stasis of ingested foods. These foods then lead to esophageal symptoms that cause dysphagia, regurgitation, chest pain, or weight loss [82].

Achalasia should be considered when other pathologies are excluded with upper GIS endoscopy in the patient presenting with dysphagia and other esophageal symptoms. In the diagnosis of achalasia, methods such as barium esophagography, real-time esophageal transit

esophagography/scintigraphy, conventional esophagus manometry, high-resolution esophagus manometry, and upper endoscopy are used.

Achalasia treatments are performed to decrease LES pressure. In medical treatment, nitrates, calcium canal blockers, and phosphodiesterase inhibitors can be used. Endoscopic injection of agents such as botulinum toxin, intermittent dilatation, or temporary stenting can be done. Another treatment is carried out by dividing the LES muscle (Myotomy) [83]. Myotomy can be performed by endoscopic (peroral endoscopic myotomy-POEM) or surgical intervention (Heller myotomy) [84, 85]. Heller myotomy can be applied by the laparoscopic or conventional method. In the laparoscopic method, an approach from thorax or abdomen can be performed. The treatment steps are started with the methods that are the least invasive and reusable. Other indications for esophageal resections are the presence of high-grade dysplasia or cancer.

Reflux occurs in 11–25% of patients after myotomy and in 2% of patients after pneumatic dilatation [86]. Adenocarcinoma may develop due to treatment-related reflux and Barrett's esophagus [87, 88]. Esophagectomy may be considered in treatment-resistant and especially Chagas-induced achalasia cases [89, 90].

13.6 Miscellaneous Conditions

13.6.1 Plummer-Vinson Syndrome

Plummer-Vinson syndrome (PVS) also known as Paterson-Brown-Kelly syndrome is characterized by a triad of iron-deficiency anemia, dysphagia, and esophageal web [91]. Decreased incidence may be due to the better nutrition status and success on iron deficiency treatment [92]. The pathogenesis of PVS is not well-known. Iron deficiency was asserted to cause dysfunction of iron-dependent enzymes and lead to oxidative stress-related DNA damages in esophageal mucosa. Repeated injury causes degradation of pharyngeal muscles and leads to the formation of esophageal webs [93, 94]. Iron supplementation is the first-step treatment. Dysphagia improves even after only iron supplementation in most of the cases. Endoscopic dilatation of the esophageal webs may be required in patients resistant to iron treatment [93]. Differentiation of PVS from other more common causes of dysphagia including malignancy, benign strictures, and corrosive esophageal burns is essential. PVS is associated with upper esophageal squamous cell carcinoma, thus endoscopic follow-up is required [95]. Esophagectomy should be considered just in case of development of a malignant tumor.

13.6.2 Tylosis

Tylosis is an autosomal dominant disease manifesting with skin thickening in the extremities and is associated with a high risk of developing esophageal squamous cell carcinoma (OSCC). Members of a limited number of families mostly from Western countries were described in the literature. Tylosis-associated OSCC mostly occurs in the sixth decade of life and in older ages. Annual esophagogastroscopy with quadratic biopsies of the esophageal lesions from onwards the early twenties is recommended for family members of affected patients. It is considered to require no interventions until the development of dysplastic changes in esophagogastroscopy [96, 97]. If a resectable tumor is detected in esophagogastroscopy, surgical treatment should be considered. Otherwise, radiotherapy and chemotherapy may be applied. An esophageal stent is a palliative option in patients with unresectable or metastatic tumors to eliminate dysphagia [96].

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14 Stomach and Duodenum Resections for Genetic Predispositions

Mustafa Özsoy and Faik Yaylak

14.1 Introduction

Gastric cancer being among the top five most common cancer types is the third leading cause of cancer-related mortalities. Despite advances in diagnosis and treatment, the 5-year survival rate is still approximately 20% [1]. In line with the histopathological classification of gastric cancers, it is divided into two categories; the intestinal-type that is predominantly related to environmental factors and rich in glandular, papillary, and tubular structures, and the diffuse-type that is predominantly related to genetic factors [2].

14.2 Overview of Gastric Cancer Carcinogenesis

About 10–20% of gastric carcinoma cases have a familial predisposition, while only a small proportion (about 1–3%) of them is associated with defined genetic tumor predisposition syndromes. Families that have BRCA1 and BRCA2 germline mutations, Lynch, Peutz-Jeghers, Li-Fraumeni syndrome, MUTYH-related adenomatous polyposis, familial adenomatous polyposis, and Cowden syndromes have a higher incidence of gastric cancer compared to the overall population [3, 4]. Gastric cancers are also one of the few malign neoplasms with an etiology on which infectious agents have a significant role. The International Agency for Research on Cancer, a part of the World Health Organization, identified *Helicobacter pylori* infection as the primary cause of gastric adenocarcinoma in 1994 [5]. An untreated pylori infection leads to a long-lasting chronic active gastritis, which is a risk factor for both intestinal and diffuse gastric adenocarcinomas. However, gastric cancer occurs only in a small portion of patients infected with pylori (3/10,000). This situation could be due to the genetic predisposition, and possible differences in bacterial strains [6]. When gastric cancer was examined, Epstein–Barr virus (EBV) was found at a higher frequency (2–16%), especially in tumors of the proximal and middle part of the stomach. Many EBV-related genes including Eber1, Eber2, Ebna1, Lmp2a, Barf0–1 were found to be associated with gastric cancer [7].

Intestinal-type and diffuse-type gastric cancers are the two distinct gastric adenocarcinomas with different morphological appearance, epidemiology, pathophysiology, and genetic profile. Unlike intestinal-type gastric cancers forming tightly linked tubular or glandular structures,

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similar to other gastrointestinal system cancers; diffuse carcinomas are predominantly characterized by invasion without the formation of tubular or glandular structures. In diffuse carcinomas, the primary carcinogenic event is the loss of E-cadherin that is an important cell surface protein for establishing intercellular connections and maintaining the organization of epithelial tissues. Intestinal-type gastric carcinomas have a better prognosis than diffuse-type gastric carcinomas. Besides, pathogenesis differences also play a role in the treatment method. Intestinal-type gastric cancers are more sensitive to 5-FU and oxaliplatin, while diffuse-type cancers are more sensitive to cisplatin [8, 9].

14.3 Intestinal-Type Gastric Cancers

Sporadic cases are more frequently seen as compared to hereditary causes. Environmental factors, such as diet, smoking, alcohol use, as well as intrinsic factors, play a role in the development of these cancers. They are usually seen at older ages, but there is a long-lasting precancerous process. Intestinal-type cancers are usually localized to the antrum or corpus being adjacent to the incisura angularis. Among the environmental factors *H. pylori* is of particular importance. The disease is found in infancy and childhood. However, clinical symptoms appear after the fourth or a later decade [10]. The induction of the carcinogenesis process is associated with oxidative stress caused by the inducible nitric oxide synthase (iNOS) produced by inflammatory cells that respond to pylori infection. Nitric oxide is mutagenic and causes abnormalities in the DNA of epithelial cells [11]. CagA secreted by pylori strains plays a role in the etiology of gastric cancer. Seven different types of pylori were identified. In Europe, the infection rate is lower due to the more dominant release of CagA secretion in isolated strains. However, the rates of gastric carcinomas are higher. In Africa, the opposite is true [12]. Many gene alterations were identified in various preneoplastic/neoplastic stages. However, the alterations do not follow a sequential order, like colorectal carcinomas [13]. Factors that play a role in gastric carcinogenesis are:

1. Oncogenes
   (a) Early K-Ras mutations: They are seen in invasive gastric cancers, dysplasia, and intestinal metaplasia. It was determined in 34% of diffuse-type cases, while in 19% of intestinal-type cases. c-erbB2 is overexpressed in intestinal cancer types, while c-met amplification and FGFR/ErbB3/PI3 kinase pathway aberrations are frequently found in diffuse-type cancers [14].
   (b) Tumor suppressor genes (TSG): In about 50% of intestinal-type gastric cancers, alterations in tumor suppressor genes such as TP53, TP73, adenomatous polyposis coli (APC), trefoil factor family, DCC, FHIT were detected. TP53 is an important regulatory factor in the cell cycle, and the loss or inactivation of its expression is the most common genetic alteration in gastric cancer. It is found in 60% of invasive tumors [15].
   (c) Loss of heterozygosity (LOH): It is a transcription factor, which has a function like tumor suppressor gene. Loh in 1p, 2q, 3p, 4p, 5q, 6p, 7p, 7q, 8p, 9p, 11q, 12q, 13q, 14q, 17p, 18q, 21q, and 22q plays an important role in gastric carcinogenesis [16].
   (d) Cell cycle regulatory molecules: Cyclin E and cyclin-dependent kinase inhibitor 1B 2 are important cell cycle regulators. Overexpression of cyclin E is common in gastric carcinomas. It may be an indicator for malignant transformation of dysplasia and tumor aggressiveness in invasive cancer.
   (e) Invasion and angiogenesis: E-cadherin plays an important role in cell motility, cell growth, and cancer invasion. VEGF-A plays a role in bone metastasis from gastric cancer, while VEGF-D plays a role in lymphatic metastasis.
   (f) micRNA: It plays a role in proliferation, apoptosis, differentiation, angiogenesis, metastasis, and immune response [17, 18].
2. Epigenetic mechanisms: DNA hypomethylation leads to the activation of oncogenes and

genome instability. However, DNA hypermethylation leads to the suppression of tumor suppressor genes and transcriptional DNA mismatch repair genes. Hypermethylation of the reprimo gene is seen in early gastric cancer specimens as well as isolated from the blood of patients. Thus, it can be used as a biomarker for determining early-stage gastric cancers. Urokinase plasminogen activator receptor (uPAR) is a biomarker secreted by macrophages, showing invasion in gastric cancer. Beta-catenin mutation is the most common cause of the activation of WNT pathway in gastric cancer. Beta-catenin mutation is determined especially in tumor-adjacent parenchyma. Cells around the tumor differentiate from mesenchymal cells to epithelial cells. Beta-catenin is responsible for the adhesion, migration, proliferation, and differentiation of cells [19, 20].

3. Genetic polymorphism: There are certain polymorphisms in gastric cancer. IL-1 beta (IL-1B) gene and IL-1 receptor antagonist gene polymorphism are associated with an increased risk of gastric cancer.
4. Chromosomal instability (CIN): It refers to a higher probability of chromosomal abnormality due to defects occurred during replication, recombination, DNA repair, chromosome separation, or at the cell cycle checkpoints. In particular, chromosomal instability is detected in sporadic gastric cancers [21].
5. Microsatellite instability: Microsatellite instability (MSI) results from the mutation of DNA repair genes such as MLH1, MSH2 which maintain genomic stability, inhibiting mutations in tumor suppressor genes. Replication defects during DNA replication such as base–base mismatches, insertion, and deletion result in the development of MSI. It is found in 15–20% of intestinal-type cancer cases, while in a higher rate in familial gastric cancer cases [21].
6. Normal stem cells: They are found in the proliferative zone of the neck/isthmus region in the normal gastric mucosa. They undergo a complex bipolar migration from there either upward or downward, becoming differentiated normal epithelial cells. They are immature, less organized, and multipotent stem cells. These cells are assumed to turn into cancer stem cells during oncogenesis [22].

14.4 Diffuse-Type Gastric Cancer

Despite the unclear complex and poor molecular pathological mechanism of intestinal-type gastric cancers, diffuse-type carcinomas are characterized by the loss of E-cadherin molecules, which are responsible for cell adhesion. It has the worst prognosis due to its rapid progression and common metastatic nature. It may fully involve the stomach wall, invade the distal esophagus and duodenum, and sometimes cause linitis plastica [23].

14.5 Familial Gastric Cancers

The incidence of familial gastric cancer is 1–3% among all gastric cancers. Currently, there are three main identified syndromes. These include hereditary diffuse-type gastric cancer, familial intestinal gastric cancer, and gastric adenocarcinoma and proximal polyposis of the stomach [24]. Gastric adenocarcinoma and proximal polyposis of the stomach is a syndrome with an autosomal dominant inheritance pattern identified in 2012. It is characterized by fundic gland polyps and dysplasia and intestinal-type adenocarcinoma foci that develop on these polyps without colorectal or duodenal polyps or other gastrointestinal cancer syndromes. There are more than a hundred fundic gland polyps less than 10 mm in size in the corpus and fundus of the stomach. The esophagus, antrum, pylorus, and duodenum are preserved. Before making a diagnosis, it should be confirmed that the patients have not used a proton pump inhibitor. The presence of point mutations in the APC gene promoter 1E should be regarded as an FAP variant of this syndrome [25]. The youngest gastric cancer case with this syndrome was reported to be 33 years old. Familial intestinal gastric cancer is defined as the clustering of intestinal-type gastric cancers

in a certain family without hereditary polyposis or cancer syndromes. The diagnosis criteria vary by the incidence of gastric cancer in that region being low or high. In countries where the incidence is high such as Korea or Japan, similar criteria were applied compared to the ones used in Amsterdam. According to these criteria, two consecutive generations should have been affected. At least three relatives should have been diagnosed with intestinal-type gastric cancer, there should be a first-degree relationship between them, and one of them should have been diagnosed before age 50 years. According to the criteria applied in countries where the incidence of gastric cancer is low such as the United Kingdom and the USA, at least two first-degree or second-degree relatives should have been diagnosed with intestinal-type gastric cancer, one of them being diagnosed before the age of 50. Moreover, at least three relatives should have been diagnosed with intestinal-type gastric cancer at any age. Familial intestinal gastric cancer has an autosomal dominant inheritance pattern. However, its genetic infrastructure has not yet been revealed [26]. Summary of familial gastric cancer is shown in Table 14.1.

14.6 Hereditary Diffuse Gastric Cancer Syndrome

Hereditary diffuse-type gastric cancer syndrome was first identified in 1964 in a New Zealand "Maori family" with 98 family members of which 28 had gastric cancer. Guilford investigated the genetic basis of the disease [27]. It was found that this type of gastric cancer, which has an autosomal dominant inheritance pattern, arises at an early age, is poorly differentiated (signet ring cells), and has been caused by CDH1 mutation. The CDH1 gene is located at 16p22.1 locus. It consists of 16 exons that disperse over about 100 kilobases and encodes a transmembrane protein called E-cadherin of 728 amino acids long. E-cadherin is a glycoprotein that is present in the epithelium of all mammals. It is within the family

Table 14.1 Summary of familial gastric cancer syndromes

	Diagnostic criteria	Genetic predisposing factors
Gastric adenocarcinoma and proximal polyposis of the stomach	1. The presence of limited polyps in the stomach corpus and fundus without colonic or duodenal polyposis 2. The number of polyps >100 or >30 proximal gastric polyps in a first degree 3. The majority of these are fundic gland polyps (some also have dysplasia) OR there is a family history of dysplasia with fundic gland polyps or gastric carcinoma	I. Germline mutation in the APC gene promoter II. Autosomal dominant
Familial intestinal gastric cancer	1. Diagnosis of intestinal type stomach cancer in three or more relatives regardless of age of diagnosis 2. Intestinal type stomach cancer in at least two first/second degree relatives, one of whom was diagnosed before the age of 50	No screening available
Hereditary diffuse gastric cancer	1. Two or more cases of gastric cancer, one confirmed case of diffuse gastric cancer in someone younger than 50 yearsThree or more confirmed diffuse gastric cancer cases in first-degree or second-degree relatives, independent of age of onset 2. Diffuse gastric cancer before age 40 years without a family history; personal or family history of diffuse gastric cancer and lobular breast cancer, one of which must be diagnosed before age 50 years	Sequencing of CDH1 coding sequences Multiplex ligation-dependent probe amplification (large CDH1 rearrangements) Sequencing of CTNNA1 coding sequences

of cell adhesion molecules and is the first identified member of this family. The intracellular portion consists of 151 amino acids and is linked to the intracellular actin cytoskeleton through α, β, and γ catenins. The extracellular portion consists of 554 amino acids and is in communication with E-cadherin molecules of adjacent cells [28]. It is an important adhesion protein for cell development, cell differentiation, and maintenance of epithelium structure. Morphological properties, such as the loss of gland structure in hereditary diffuse gastric cancer due to E-cadherin mutation and the loss of cell polarity, support the role of this protein. It has been also associated with CDH1 mutation in cleft lips/palates being a congenital midline defect [29]. Currently, there are over 120 identified CDH1 gene mutations. The mutations may affect the synthesis, intracellular position, and function of E-cadherin. The most common mutation is small frameshift mutations (37.5%) followed by "splice-site," "non-sense," "mis-sense" mutations, and major displacements. In carriers with one mutant allele, the loss of other allele due to a secondary effect such as hypermethylation of the promoter region and loss of heterozygosity initiate the process of gastric cancer development. CDH1 gene mutation is determined in 25–50% of families with hereditary diffuse gastric cancer. This mutation is passed to the next generation by autosomal dominant inheritance [30].

14.6.1 Diagnosis

The average age at diagnosis of hereditary diffuse gastric cancer is 38 years. Among the reported cases, the youngest one was 14 years old and the oldest one was 82 years old. Although individuals diagnosed with early-onset gastric carcinoma have been reported, the risk of cancer before age 20 years is considered low. The risk for diffuse gastric carcinoma is 67–70% for men and 56–83% for women by the age of 80 [31]. The presenting complaints include weight loss, abdominal pain, nausea, loss of appetite, early satiety, and melena. Metastatic patients may have hepatomegaly, ascites, jaundice, skin nodules, and pathological fractures. The majority of patients with hereditary diffuse gastric cancer syndrome is diagnosed in an advanced stage when it presents as "linitis plastica." The youngest patient who was a CDH1 mutation carrier and underwent prophylactic total gastrectomy was 16 years old [31]. Prophylactic total gastrectomy specimens from mutation carriers are almost always macroscopically normal [32]. Thus, the whole stomach should be carefully examined in the pathological examination of prophylactic gastrectomy specimens. The risk of lobular breast cancer is 42% for women who are a CDH1 gene mutation carrier. The diagnosis criteria for hereditary diffuse gastric cancer syndrome were first established by Gastric Cancer Linkage Consortium in 1999 and revised in 2010 and 2015 [33–35]. Accordingly, the diagnosis criteria are:

1. The presence of two cases with gastric cancer, regardless of age, with one having diffuse-type gastric cancer.
2. A case of diffuse gastric cancer before age 40.
3. A personal or family story of diffuse gastric cancer or lobular breast cancer, with one case diagnosed before age 50.

In the 2015 version, the consortium identified the families for which genetic testing may be considered, even though they do not meet these criteria, as follows [35]:

1. Bilateral lobular breast cancer or at least two cases of breast cancer diagnosed at age less than 50 years.
2. Personal or family history of cleft lip or palate in a patient with diffuse gastric cancer.
3. In situ signet ring cells or pagetoid spread of signet ring cells.

More than one in situ and T1a carcinoma foci have been found in nearly all of over 100 prophylactic total gastrectomy specimens so far [33–35]. This reveals the following two results. In all CDH1 gene mutation carriers, in situ and T1a carcinoma foci cannot reach a further stage. There is no certain time of period for the existing in situ and T1a carcinoma foci to reach a T1b

stage or further stage; however, this period may be excessively prolonged in some patients. The known oldest asymptomatic carrier was 75 years old, while the youngest individual who died of gastric cancer was a 14-year-old male. Given the foci in prophylactic gastrectomy specimens, the risk of progression of the early foci to apparent gastric carcinoma was found 0.5% [36]. The 5-year survival rate in patients who have been diagnosed and operated at an early stage is higher than 90%. This rate reduces to 20% in patients who have been diagnosed at an advanced stage [37]. This emphasizes the importance of early diagnosis and treatment, even prophylactic interventions.

It is essential to identify asymptomatic mutation carriers to reduce the morbidity and mortality of hereditary diffuse gastric cancer. The optimal age for starting genetic screening, how the affected individuals will be followed up, or whether prophylactic interventions will be performed are controversial topics. Although the risk of gastric cancer is below 1% before age 20, the International Gastric Cancer Linkage Consortium recommends for individuals with a family history of early-onset diffuse gastric cancer to have a genetic test between 16 and 18 years old [38]. The most important thing for individuals with identified CDH1 gene mutation is what the next step will be. Currently, there are two approaches to the risk of gastric cancer. These are close endoscopic follow-up and prophylactic gastrectomy.

14.6.2 Endoscopic Follow-Up

The role of endoscopic follow-up in CDH1 gene mutation carriers is to postpone the surgery as much as possible to protect the stomach. The major basis for those who advocate close endoscopic follow-up is the fact that the penetrance rate of the disease is 80%. Accordingly, 20% of CDH1 gene mutation carriers who underwent prophylactic gastrectomy have been unnecessarily operated. On the other hand, the intact mucosa over the early foci usually makes their identification difficult and reduces the effectiveness of the procedure [39]. Identifiable foci are seen as millimetric regions that are paler than normal mucosa. The International Gastric Cancer Linkage Consortium listed the endoscopy indications in the consensus report version 2015 as follows [35]:

- Those who refuse prophylactic surgery.
- Mutation carriers who are younger than the age (approximately 20 years) at which prophylactic surgery is recommended.
- Pre-prophylactic surgery for newly diagnosed carriers.

The starting age of endoscopic follow-up is between 16 and 18 years, as in mutation screening. It is important to perform 6- and 12-month follow-ups in experienced centers. The consensus recommends performing a careful examination for at least 30 min. A total of at least 30 biopsy procedures should be performed in prepyloric area, antrum, corpus, fundus, and cardiac regions to increase the diagnostic value. In a cohort study conducted by Lim et al. in 2014, the sensitivity of endoscopic biopsy was calculated 64%. A chromoendoscopy using the congo red methylene blue increases the sensitivity of the scan [40].

14.6.3 Prophylactic Gastrectomy

According to the data obtained so far, for CDH1 mutation carriers, the risk of death from gastric cancer in the mid-twenties exceeds the risk of mortality from total gastrectomy (1%) performed at the same age. Thus, the selective method to be recommended for mutation carriers considering the limitations of endoscopy is the prophylactic total gastrectomy. The prophylactic gastrectomy option is often offered to mutation carriers after age 20. However, another approach is to perform prophylactic surgery 5 years before the earliest age of diagnosis of gastric cancer in the family. In women, total gastrectomy may be postponed due to its effects on a future pregnancy; however, it is recommended to be performed before age 40 if possible [41]. The surgery method is total gastrectomy and Roux-en-Y esophagojejunostomy.

The consensus decision about lymph node dissection is to perform D1 dissection. Since the main purpose of prophylactic gastrectomy is the complete removal of the stomach mucosa, both the esophagogastric junction and the gastroduodenal junction should be removed. Another important point to be emphasized here is Meckel's diverticulum. Since it may contain the gastric mucosa, the presence of Meckel's diverticulum should be investigated in each individual who underwent prophylactic gastrectomy, and in this case, diverticulectomy should be performed [42, 43].

14.7 Duodenum Resections for Genetic Predispositions

Small intestine tumors account for 1% of all gastrointestinal system tumors [44]. This has been associated with the liquid content of the small bowel being higher than that of the column, less exposure of the small intestine mucosa to carcinogen substances due to faster transit time, the alkaline nature of the small intestine, and the presence of intense secretory immunoglobulins. Thus, tumors of the small intestines are less frequently encountered than that of the gastrointestinal system. Benign small intestine tumors are very rare, and the majority of them are located in the duodenum [45]. The most common benign small intestine tumors are Brunner's gland tumors, adenoma, inflammatory polyp, lipoma, arteriovenous malformation, and lymphangiectasis. Adenocarcinoma is the most common malignancy of the small intestine. The ampulla of Vater is located at the union of the pancreatic and biliary ducts on the walls of the duodenum. Although it covers a small area, it is the region with the highest incidence of neoplastic transformation within the small intestine. The risk of small intestine adenocarcinoma increased with Crohn disease, gluten enteropathy, Peutz-Jeghers syndrome, and familial adenomatous polyposis (FAP) syndrome. Ampullary adenomas or cancers may be present in the form of sporadic lesions or with FAP [46].

Familial adenomatous polyposis is an autosomal dominant disease resulting from a defect in the adenomatous polyposis coli (APC) gene [47]. The APC gene is a tumor suppressor gene mapped in the long arm (5q21) of chromosome 5. The APC gene is the gene controlling the Wnt pathway. When the Wnt pathway is stimulated, cell proliferation increases. If both alleles are inactivated as a result of APC mutations, the control over the Wnt pathway is removed. This pathway always remains open, causing uncontrolled cell division. Hundreds of premalignant adenomas develop in the colon and rectum, conferring an almost 100% lifetime risk of colorectal cancer. Prophylactic colectomy is recommended in early adulthood to prevent the development of colorectal cancer. FAP is also associated with several extracolonic manifestations including osteomas, epidermoid cysts, dental abnormalities, hypertrophy of the retinal pigment epithelium, desmoid tumors, adenomas of the upper gastrointestinal tract, and many malignancies [48]. One of the most important of these is the duodenal polyposis. Individuals with FAP have nearly a 100% lifetime risk of developing duodenal polyposis. Duodenal adenomas have a similar biology to colorectal adenomas and are considered to progress as cancer via an analogous adenoma–carcinoma sequence. While the risk of developing duodenal cancer with FAP is 100–330 times without FAP, the absolute lifetime risk is 4–10%. Nevertheless, duodenal cancer is the second leading cause of mortality in individuals with FAP after colorectal cancer [49, 50].

The degree of duodenal polyposis can be tracked by endoscopy with biopsy and can be quantified using the Spigelman staging scale (Table 14.2). A method used for determining the risk of cancer in ampullary adenomas with FAP is the Spigelman system that has been established based on the number, size, and histology of polyps in the duodenum. The sum of these scores is converted into a stage rating from 0 to IV with stage 0 corresponding to no polyposis and stage IV corresponding to severe polyposis. The risk of developing cancer increases with the high Spigelman stage [51]. Endoscopic treatment may be administered after resection at Spigelman stage II and III provided that a close endoscopic follow-up. Currently, endoscopic screen-

Table 14.2 Modified Spigelman Scoring System

	Score			
	1	2	3	Staging by score
Number of polyps	1–4	5–20	>20	Stage 0 (none polyp) Stage 1 → 1–4 score Stage 2 → 5–6 score Stage 3 → 7–8 score Stage 4 → 9–12 score
Polyp size (Mm)	1–4	5–20	>10	
Histology	Tubular	Tubulovillous	Villous	
Dysplasia	Mild	Moderate	Severity	

ing is recommended every 5 years to 6 months. There are Spigelman stage IV adenomatosis and ampullary lesions in the duodenum in 10–30% of patients with FAP. The risk of cumulative cancer is approximately 30–40% for these patients, and prophylactic pancreaticoduodenectomy is recommended [52]. PD is a major operation with substantial morbidity and mortality. While taking the decision of whether to undergo prophylactic surgery, patients with FAP and duodenal polyposis should balance potential risks and benefits. If surgery is pursued too aggressively, the patient risks surgical mortality and morbidity when cancer might not have developed. Unless surgery is pursued aggressively enough, the patient risks the development of preventable cancer.

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15 Prophylactic Surgery for Benign Diseases of Stomach and Duodenum

Nuru Bayramov and Nadir Zeynalov

15.1 Introduction

This chapter is dedicated to prophylactic surgeries for some benign diseases of stomach and duodenum, and the indications to such procedures according to data from up-to-date literature. The main focus is on gastric and duodenal diverticula, postoperative delayed gastric emptying, hiatal hernia, gastroesophageal reflux, reflux gastritis, gastroesophageal anastomosis leakage, and gastric volvulus. Brief information on prophylactic gastroenterostomy, gastric partitioning, pyloroplasty, vagotomy, and gastrostomy is given as well.

15.2 Prophylactic Gastrojejunostomy

Lesions around ampulla of Vater are non-resectable in about 70% cases by the time they are found, and about 70% cases are presented by obstructive jaundice [1]. After application of palliative biliary drainage in 19–42% of cases, a gastric outlet obstruction develops demanding repeated intervention [2, 3]. That's why the question of application of prophylactic gastrojejunostomy together with biliary drainage in patients with non-resectable periampullary lesions and no gastric outlet obstruction is quite relevant. However, there are also concerns about possible increase of morbidity and mortality because of prophylactic gastrojejunostomy. In two randomized studies, the patients with periampullary lesions intraoperatively evaluated as non-resectable (extensive vascular invasion and metastases) were divided to a group with bilioenteric anastomosis only (single bypass group) and a group with biliary and gastric bypass (double bypass group) [2, 3]. The comparison of the results shows that addition of prophylactic gastrojejunostomy to bilioenteric bypass surgery does not increase the rate of complications, mortality, life expectancy, and quality of life, and significantly reduces the rate of gastric outlet obstruction and need for repeated intervention. In the single bypass group 19% and 42% of patients, and in the double bypass group 0% and 6% of patients developed gastric outlet obstruction after surgery. Some authors advocate prophylactic biliodigestive and gastroenteric bypass procedure even in patients with non-resectable periampullary lesions without biliary or gastric obstruction in order to prevent it in future and provide uninterrupted chemotherapy [4]. There are many surgical procedures for biliary and gastric bypass, but the most advised is the Roux-en-Y loop for bilioenteric anastomosis, and antecolic or retrocolic gastroenterostomy on afferent or efferent loop.

Thus, the addition of gastrojejunostomy to bilioenteric bypass procedure in patients with

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periampullary lesions intraoperatively evaluated as non-resectable can be recommended in order to prevent gastric obstruction in future.

15.3 Prophylactic Partial Stomach-Partitioning

Gastrojejunostomy is a common method of surgical bypass for palliation in non-resectable malignant gastric outlet obstructions. However, in 30–50% of cases it results in a syndrome called delayed gastric emptying, or gastric stasis presented by belching, vomiting, and intolerance to oral feeding [5, 6]. Among methods of prevention of delayed gastric emptying, there is a complete or partial stomach-partitioning additionally to gastrojejunostomy (Fig. 15.1). In complete partitioning (Devine exclusion procedure) the distal part of stomach is transected and closed, and in partial partitioning (modified Devine exclusion) 2–3 cm connecting bridge between the distal and proximal parts of stomach is left for decompression and endoscopic interventions [7, 8].

Though there are no randomized studies about the effect of gastrojejunostomy with stomach-partitioning to delayed gastric emptying, there are many clinical observations and meta-analyses on this topic. Two meta-analyses conducted in the recent years [9, 10] raised a special interest by comparing gastrojejunostomy with complete or partial stomach-partitioning and conventional gastrojejunostomy. It has been shown that gastrojejunostomy with stomach-partitioning significantly reduced the rate of postoperative gastric stasis (11.6% vs. 43.6%), improved the oral feeding and tendency of life expectancy, and did not increase the operation time and intraoperative bleeding. Experience of laparoscopic implementation of these operations has been growing over the past years [11, 12].

So, the meta-analysis of non-randomized and cohort studies shows that in order to decline the rate of delayed gastric emptying following palliative gastrojejunostomy in patients with non-resectable obstruction of gastric outlet gastrojejunostomy can be added by complete or partial stomach-partitioning.

15.4 Prophylactic Pyloric Interventions

Pyloroplasty is a surgical procedure of transection of pyloric sphincter. It is applied as a treatment modality in pyloric stenosis, and as a prophylactic procedure to prevent spasm of pyloric sphincter and delayed gastric emptying which are the complications after esophageal surgery [13].

Vagotomy, dislocation of stomach to the negative pressure thorax, and imbalance of gastrointestinal hormones result in functional disorders in about half of the patients, more often delayed gastric emptying (gastric stasis), duodenogastroesophageal reflux, and dumping syndrome [14, 15].

Taking into account that the main cause of delayed gastric emptying is the absence of relaxation of pylorus because of vagotomy, pyloroplasty is routinely applied in vagotomy for peptic

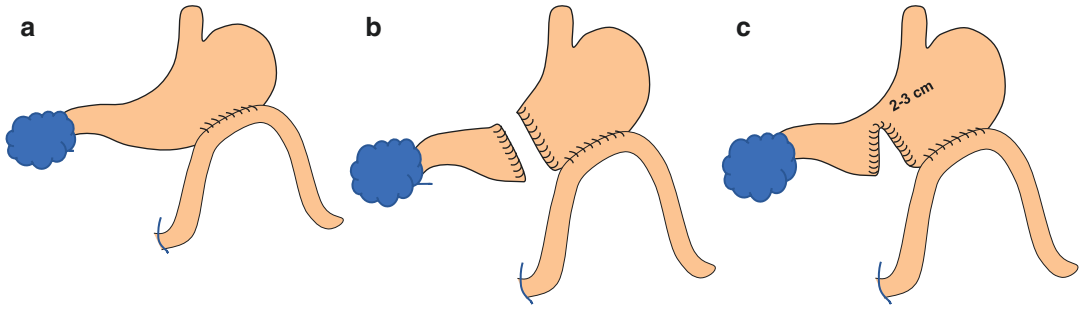

Fig. 15.1 (**a**) Gastrojejunostomy, (**b**) complete stomach partitioning and gastrojejunostomy, (**c**) partial stomach partitioning and gastrojejunostomy

ulcer disease and intraoperative injuries of vagus nerve (anti-reflux procedures, hiatal hernia surgery, etc.). However in clinical practice the significance of prophylactic pyloric interventions during gastroplasty after esophagectomy is still a subject for discussion.

Functional obstruction of stomach and according delayed gastric emptying are noted in 15–39% cases after esophagectomy with gastroplasty [16], there are also reports on decline of this rate for the recent years because of wide application of stomach tube [17, 18]. It is clinically presented by early satiety, postprandial discomfort, dysphagia, belching, and regurgitation; aspiration pneumonia and reflux esophagitis are possible complications. Treatment includes diet, erythromycin which is the agonist of motilin, and pyloric interventions (pyloroplasty, pyloromyotomy, balloon dilatation, botulinum injection) [14, 16].

In previous years, especially before 2007 randomized studies and meta-analyses showed that pyloroplasty following esophagectomy significantly reduced the rate of postoperative delayed gastric emptying, but had no effect on rates of pulmonary complications, leakage of anastomosis, and other results [19–21].

However, retrospective and systematic studies for the past decade show that pyloroplasty does not significantly change the rates of delayed gastric emptying, reflux esophagitis, pulmonary complications, and anastomosis leakage [16, 22, 23]. Moreover, some studies report that pyloroplasty increases bile reflux and operation time [23]. It is quite difficult to explain the differences between these two groups of studies. Some authors suggest that open surgery and procedure with total stomach have been used before, while minimally invasive methods and procedure with gastric tube are being used for the recent years [16]. That's why there is a need for new randomized studies on minimally invasive esophagectomy and application of gastric tube [14, 16].

There is no common idea about the method of pyloric drainage as well. Clinical studies showed no significant difference in efficacy of pyloroplasty, pyloromyotomy, and botulinum injection [15].

Thus, prophylactic pyloroplasty for prevention of delayed gastric emptying seems reasonable in cases of vagotomy and damage of vagus nerve at surgery, but its significance in case of gastroplasty after esophagectomy remains disputable. In open surgery with total stomach reconstruction, pyloric interventions seem beneficial. However, pyloric interventions do not seem so in procedures with gastric conduit which are applied for the recent years—they increase the bile reflux. New multicenter randomized studies are necessary to clarify these questions.

15.5 Vagotomy

Vagus nerve is the important regulator of secretion of gastric acid [13]. The main purpose of transection of vagus nerve (vagotomy) is the reduction of secretion of gastric acid to prevent the relapse and complications of peptic ulcer. This surgical procedure is rarely applied alone, instead it is usually done together with gastric drainage and resection operations. Vagotomy has been widely used in surgical management of peptic ulcer disease before the era of H2 histamine receptor blockers, proton pump inhibitors, and anti-helicobacter therapy. Nowadays, the application of vagotomy slumped dramatically; it can be applied according to the following indications: ulcers resistant to conservative management, complications of peptic ulcer disease (stenosis, bleeding, perforation), and prevention of peptic ulcer of gastroenteroanastomosis [24].

According to the level of transection, vagotomy can be truncal (vagus nerve is transected at the level of esophagus), gastric or selective (branches of vagus nerve to stomach are transected), and highly selective (branches of vagus nerve to body of stomach are transected while branches to antrum and pylorus are spared). Vagotomy can be done by open surgery or laparoscopically [24].

15.6 Prophylactic Gastrostomy

Gastrostomy is a procedure for transabdominal access to stomach. It can be done by surgical, percutaneous, endoscopic, and combined methods.

Gastrostomy is a treatment modality for patients with difficult oral feeding (cancer of head, neck, thorax, esophagus, brain injury) or for decompression of stomach (delayed gastric emptying, short bowel syndrome). Indications to prophylactic gastrostomy are very limited, they include duodenal injuries and large pyloric perforations in order to provide a stomach decompression, and gastric volvulus in order to fix the stomach [25].

15.7 Preoperative Ischemic Conditioning of the Stomach

The ground of the idea of gastric conditioning is the phenomenon of preparation of stomach to ischemia before applying the esophagogastric anastomosis in order to reduce the anastomosis leakage risk. The most widely used method of reconstruction after esophagectomy is esophagogastric anastomosis with gastric conduit. This type of anastomosis is considered to be of high risk of leakage. According to universally accepted opinion and data of recently conducted sensitive studies, the ischemia in the site of anastomosis is one of the strongest risk factors for leakage [26]. Typical process of preparation of gastric conduit includes the ligation of left gastric artery, short gastric arteries, and sometimes right gastric artery, remaining the blood supply of gastric conduit by right gastroepiploic artery and submucosal vascular network. Studies show that this standard mobilization results in more than 50% decrease of perfusion of upper 20% of the stomach [27]. Experimental works revealed that acute hypoperfusion after partial devascularization results in ischemic injury of the stomach after 3–5 days. After 10 days the perfusion starts to recover, and after 2–3 weeks it is close to the initial perfusion rate [28–30]. According to this phenomenon of preparation to ischemia, the idea of "initial partial devascularization of stomach, then waiting few days for normalization of perfusion, then applying anastomosis" came out. By the way, this phenomenon is well known in plastic surgery; it is widely used for staged skin grafting.

Currently, there are two methods of preparation of stomach tube to ischemia: embolization of vessels and surgical ligation. In the first modality, an endovascular approach is used to embolize the left gastric artery, and sometimes additionally the right gastric artery; after 2 weeks esophagectomy is done and esophagogastric anastomosis applied [31]. In the second modality, a laparoscopic approach is used to ligate the left, right, and short gastric arteries, and apply a feeding jejunostomy if needed; then after 5–14 days the esophagectomy is done and esophagogastric anastomosis applied [32].

Clinical studies give controversial outcomes of the impact of ischemic conditioning to the rate of anastomosis leakage. Some of studies report a significant reduction of the anastomosis leakage after ischemic conditioning: 0–13% in cases with conditioning vs. 16–46% in cases without conditioning [33–36]. Other clinical studies report that in comparison with the control group the group with ischemic conditioning shows a tendency to reduction in anastomosis leakage rate without statistical significance: 8.5–26% vs. 7.6–21% accordingly [32, 37, 38]. Systematic reviews, meta-analyses, and randomized studies have also not shown a significant reduction of rate of esophagogastric anastomosis leakage after ischemic conditioning [30, 39, 40].

The results of a randomized study dedicated to this problem showed that the perfusion of both ischemic conditioned and not conditioned stomach conduit after dislocation to neck decreased 60% in comparison with the normal rate, and the difference in perfusion between the groups was not statistically significant [40]. This fact indicates a very important role of dislocation to neck in reduction of perfusion of stomach tube and can explain the uselessness of ischemic conditioning. Some studies report that ischemic conditioning reduces the severity of anastomosis leakage [37, 39].

Comparative analyses of methods of ischemic conditioning do not reveal serious differences between embolization and laparoscopic ligation [39]. Along with this such disadvantages of ischemic conditioning like undergoing surgery twice, expensiveness, and risk of complications are also reported [30].

Thus, despite ischemic conditioning of stomach tube for reconstruction after esophagectomy

seems reasonable as per some fundamental and clinical studies, many other studies report that this approach does not reduce the rate of anastomosis leakage significantly, limiting only with a tendency to decrease the severity of leakage, demands additional intervention and expenses, and carries some risk of complications.

Considering this information the method of ischemic conditioning of stomach conduit for reconstruction after esophagectomy is currently not recommended for wide application.

15.8 Gastroesophageal Reflux Disease (GERD)

GERD is the most common gastrointestinal disease; its incidence rate varies 2.5–33% among world population [41]. This disease is presented by signs related to reflux of gastric content mainly to esophagus, but also to mouth and lungs, clinically resulting in erosive esophagitis, non-erosive reflux, Barret's esophagus, and extraesophageal complications [42]. Contemporary management of GERD encompasses conservative, surgical, and endoluminal modalities. The main treatment modality is conservative management which includes change of lifestyle (sleeping with elevated bedhead, reduction of amount of each food intake, weight loss) and drug therapy (proton pomp inhibitors (PPI), H2 histamine receptor blockers, antacids, etc.). However, in about 40% of patients conservative management does not give sufficient response (refractory reflux), or side effects of pharmacotherapy arise [43]. Laparoscopic fundoplication is the main procedure in surgical management of GERD. Nissen fundoplication (360°) and Toupet fundoplication (270°) are the most commonly used operations. Fundoplication gives sufficient effect in those patients who show good outcome of PPI treatment. Forty to eighty percent of patients have to continue PPI treatment after fundoplication, and overall number of fundoplications decreased for the recent years [44]. Nowadays, fundoplication procedure is considered to be the most effective approach in following cases: side effects of drug treatment, patients refusing from pharmacotherapy, large hiatal hernia, low esophageal pH despite high dose PPI, sufficient effect achieved only by continuous high dose of PPI [42, 43]. Other surgical methods are magnetic ring (Linx™) and endoluminal procedures (transoral incisionless fundoplication, Stretta procedure) which are positioned as promising alternative methods in refractory reflux [43]. However, these new techniques need wide randomized investigations.

Another issue is the prevention of reflux after gastrointestinal surgery. Prophylactic fundoplication is routinely advised in myotomy due to achalasia and paraesophageal hernia surgery [45, 46].

So, conservative approach to management of GERD (lifestyle change, PPI, H2 histamine receptor blockers, antacids) is the main treatment modality at the moment; fundoplication is applied according to indications, and promising new surgical and endoluminal techniques need thorough investigation.

15.9 Hiatal Hernia

Hiatal hernia is considered to be of quite prevalent pathologies; it is described as dislocation of abdominal organs to the thoracic cavity through hiatal foramen of diaphragm. According to content of hernia and place of gastroesophageal junction, hiatal hernias are divided to sliding and paraesophageal hernias, and also classified to 4 types:

- Sliding or type I hernia—gastroesophageal junction is dislocated to thorax.
- Paraesophageal hernia is a complete hernia with existing hernia sac; it can be in 3 variants:
  - Type II—gastroesophageal junction does not dislocate, gastric fundus herniates up; this type is also called "pure" paraesophageal hernia.
  - Type III—both gastroesophageal junction and stomach are dislocated to thorax; this type is also called "mixed" paraesophageal hernia.
  - Type IV—hernia content is presented by stomach and other abdominal organs.

Most of hiatal hernias are sliding hernias (95%), and most of paraesophageal hernias are mixed hernias (type III) [47]. In the vast majority of patients with sliding hernia, there are no symptoms, and those with symptoms are typically presented by signs of GERD.

Paraesophageal hernias most commonly develop after surgery around the gastroesophageal junction. Despite many of such hernias are asymptomatic, some patients complain of mild gastrointestinal symptoms (epigastric pain, early satiety, bloating, hiccups). Some paraesophageal hernias can complicate by gastric volvulus, bleeding, strangulation, ileus, perforation, and respiratory failure. Endoscopy, contrast X-ray and CT are typically used for diagnosis of hiatal hernia.

Approach to management is based on type of hernia, symptoms, and complications. Symptomatic sliding hernia is managed similarly to GERD—initial treatment is conservative (lifestyle change, PPI, H2 receptor blockers, antacids), second-line treatment is surgical or by other interventions [42]. Intervention is not recommended in asymptomatic sliding hernia; however, prophylactic diaphragmatic crural repair is advised if a bariatric procedure is done (sleeve gastrectomy, Roux-en-Y bypass) [48]. Paraesophageal hernia could be a subject to urgent, planned or prophylactic surgery. Complications (gastric volvulus, bleeding, strangulation, ileus, perforation, respiratory failure) demand urgent surgery, and symptomatic cases without complication need planned operation. Prophylactic intervention in patients with asymptomatic paraesophageal hernia is controversial. Though some authors advocate prophylactic surgery, especially in large and type IV hernias because of risk of complications [49], this approach is not applied widely. The main steps in surgical technique for paraesophageal hernia are: moving the hernia content back to abdominal cavity, dissection and removal of hernia sac, placing gastroesophageal junction back to abdomen, fundoplication (total or partial), repair of hernia ring, and fixation of stomach [50]. This operation can be done laparoscopically, by laparotomy or thoracotomy. Sutures and mesh can be used for repair of hernia ring. Types of mesh and indications to its application are not specified yet. Some authors consider that repair with mesh reduces the recurrence rate, so they advise its application in most of such patients [50]. At the same time other authors recommend a selective application of mesh, taking into account possible risks of mesh-related complications [51]. The type of mesh is another unspecified topic. According to the general trend biological patch is the first choice, and absorbable and non-absorbable synthetic patch is the second choice [46, 52].

Thus, symptomatic and complicated hiatal hernia is considered to be the indication to surgery. In asymptomatic cases, surgical repair is indicated during bariatric procedures, large and type IV hernias. The use of patch/mesh has not been specified yet.

15.10 Reflux Gastritis

Reflux gastritis is a chemical gastritis occurring because of regurgitation of duodenal or jejunal content back to stomach. It usually develops after surgical procedures resulting in dysfunction of pyloric sphincter, its removal or bypassing. Sometimes it can be a primary functional disorder in patients without prior surgery. Reflux gastritis is clinically presented by pain and biliary vomiting. Conservative management (PPI, antacids, astringents, prokinetics) is effective in most cases. Surgery is indicated in refractory cases with no effect of conservative treatment. Main surgical procedures are Roux-en-Y gastric resection, Braun anastomosis, isoperistaltic jejunal interposition, and duodenal switch [53].

15.11 Gastric Volvulus

Gastric volvulus is a rare pathology related to rotation of stomach around its axis or the mesentery axis, can clinically progress in acute and chronic (recurrent) types. Acute type is presented by signs of complete gastric obstruction, leading to gastric necrosis and perforation in 1/3 of patients, may result in high mortality (30–50%) [53, 54]. Chronic type is presented by repeating

signs of gastric obstruction. Gastric volvulus can be a primary pathology; however, in most cases it is presented together with concomitant abdominal disorders, especially hiatal hernia and defects of diaphragm (secondary volvulus). Acute volvulus is typically presented by acute pain, belching, and impossibility of passage of nasogastric tube. Signs of sepsis may arise in delayed cases. CT plays the main role in diagnosis of gastric volvulus. Endoscopy is done in an operating room for evaluation of changes of mucosa and decompression [53, 54]. First-line treatment in acute volvulus is urgent stabilization of the patient and surgery. Endoscopic, laparoscopic, and open methods are used for management [55]. Urgent gastric resection is indicated if signs of necrosis of gastric wall are found at clinical examination, CT, and endoscopy (sepsis, air in or around the gastric wall, necrotic mucosa). If no such signs are found, then operation of detorsion, decompression, and gastric fixation (gastropexy) is applied. Hernioplasty and fundoplication are usually added in secondary volvulus. In order to prepare high-risk surgical patients to intervention, the surgery can be postponed for few days after successful endoscopic detorsion and decompression if there are no signs of necrosis of gastric wall.

Endoscopic percutaneous gastrostomy and gastropexy can be applied in children [25]. Surgical fixation of stomach can be done by fundo-antral gastrostomy (Opelzer's procedure), gastroenterostomy, gastric resection, simple gastropexy (suturing of stomach to abdominal wall), and gastropexy with division of gastrocolic omentum (Tanner's procedure). Though less invasive laparoscopic gastropexy is reported to have a high recurrence rate [54]. Prophylactic gastropexy is recommended in chronic gastric volvulus [53, 56].

15.12 Prophylactic Surgery for Diverticula

Gastric diverticulum is one of the rarest pathologies; it is found at radiologic investigations at 0.04%, endoscopic investigation 0.01–0.11%, and autopsies 0.02% rate [57]. Most of gastric diverticula are congenital disorders with asymptomatic progression found occasionally at investigations. Symptomatic diverticula are presented by non-specific gastrointestinal symptoms—epigastric pain (18–30%), postprandial discomfort, early satiety, nausea, vomiting, halitosis, anorexia, etc. [58, 59]. Gastric diverticulum may result in complications like ulceration, bleeding, perforation, and even malignant transformation.

Conventional approach to asymptomatic diverticulum is observation, and to symptomatic or complicated diverticulum is management, having laparoscopic resection as a first choice. Taking into account that diverticula greater than 4 cm are of high risk of complications, some authors advise the resection of such diverticula even if asymptomatic [60, 61].

It must be noted that the vast majority of scientific literature on gastric diverticula encompass small series of patients and reviews. Elaboration of common approach to small and asymptomatic diverticula demands large series of long-term studies.

Duodenum is the most common location of gastrointestinal diverticula after colon; endoscopic investigations find duodenal diverticula in 4.7–13% cases [62]. Most of duodenal diverticula are asymptomatic, but in 10% cases may be symptomatic, sometimes resulting in complications like perforation, bleeding, biliopancreatic obstruction, duodenal obstruction, and even malignant transformation; some types of duodenal diverticula may complicate ERCP procedures [63, 64]. Symptomatic and complicated duodenal diverticula need conservative and surgical treatment [64–66]. Methods of surgery vary from simple diverticulectomy to extensive procedures like duodenal resection, duodenal exclusion, and pancreaticoduodenal resection [63, 64].

Most of the authors do not recommend prophylactic interventions in duodenal diverticula because of low risk of change to symptomatic and complicated types, and high surgical risk [64, 65]. However, this conclusion is based on series with small number of patients, that's why studies with wide and large series of patients are necessary.

15.13 Conclusion

- Prophylactic gastrojejunostomy can be applied additionally to bilioenteric bypass in periampullary lesions intraoperatively evaluated as non-resectable.
- Complete or partial stomach-partitioning can be added to palliative gastrojejunostomy in patients with non-resectable obstruction of gastric outlet for prevention of delayed gastric emptying.
- Prophylactic pyloroplasty for prevention of delayed gastric emptying seems reasonable in cases of vagotomy and damage of vagus nerve at surgery, but its significance in case of gastroplasty after esophagectomy remains disputable.
- Prophylactic vagotomy may be used for prevention of peptic ulcer of gastroenteroanastomosis.
- Prophylactic gastrostomy may be reasonable in duodenal injuries, large pyloric perforations, and gastric volvulus.
- Prophylactic ischemic conditioning of stomach conduit for reconstruction after esophagectomy is currently not recommended to use widely.
- Prophylactic anti-reflux surgery is recommended in Heller myotomy and paraesophageal hernia.
- Prophylactic surgery for GERD and sliding hiatal hernia is advised during bariatric procedures, and in large and type IV hernias.
- Prophylactic Roux-en-Y, Braun, and duodenal switch procedures are recommended for prevention of reflux gastritis after gastroduodenal surgery.
- Prophylactic gastropexy is indicated in chronic gastric volvulus.
- Prophylactic surgery is recommended in large (greater than 4 cm) gastric diverticula, and not recommended in asymptomatic duodenal diverticula.

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Prophylactic Surgery for Small Intestines

16

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16.1 Introduction

In this chapter, aim and rationale of prophylactic surgery for small intestines will be discussed. Initially we will overview the types of prophylactic small intestinal surgery. In this overview, we have classified the prophylactic small intestinal surgeries according to aim and rationale. The primary aim of prophylactic small intestinal surgery is to prevent loss of small intestinal integrity and functions. The secondary type was defined those surgical procedures where small intestines are used to serve as an access point for gastrointestinal tract or to drain gastrointestinal secretions. In addition, the role of minimal invasive surgery techniques has been mentioned.

16.2 Overview of Prophylactic Small Intestinal Surgery

The primary aim of prophylactic small intestinal surgery is to prevent a further or future loss of small intestinal anatomical and functional integrity. Hernia repair in an asymptomatic patient is performed in selected patients to prevent intestinal strangulation related complications. In addition, resection of an incidental Meckel's diverticulum may be performed with the intention of minimizing future diverticulum related complications. Some other prophylactic surgical procedures may involve small intestines to access gastrointestinal system or to divert gastrointestinal secretions to feed or to prevent a gastrointestinal leak and related conditions. This chapter will focus on these main domains of prophylactic small intestinal surgery.

16.3 Types of Prophylactic Surgeries for Small Intestines

Prophylactic surgeries for small intestines may be of mainly two types. The primary type of prophylactic surgeries for small intestines has intended to protect small intestinal continuity and functional integrity. This type of prophylactic surgeries may also intend to prevent possible small intestinal related complications such as bleeding, obstruction perforation, and even development of cancer.

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Table 16.1 Types, procedures, aims, and rationale for prophylactic surgery of small intestines

Type prophylactic surgery	Procedure	Aim and rationale for prophylaxis	Ref
Primary	Hernia repair	To prevent hernia-related strangulation in asymptomatic patients with any abdominal wall hernias, which may cause intestinal loss and merit resection	[1–3]
	Intestinal resection	To prevent complications related to Meckel's diverticulum in asymptomatic patients	[4–10]
	Endoscopic or surgical drainage	To prevent duplication cyst related mass effect. Cyst is drained, a partial cyst removal or fenestration may be performed	[11, 12]
	Endoscopic or surgical polypectomy	To prevent cancer development in polyposis syndromes	[13, 14]
	Closure of omental or mesenteric openings	To prevent internal herniation after a gastric bypass surgery for obesity surgery	[15, 16]
Secondary	Loop ileostomy	Decompression of a distal ileoanal or ileorectal anastomosis after a total proctocolectomy of colectomy, or a colorectal or coloanal anastomosis after an anterior resection	[17–20]
	Feeding jejunostomy	Endoscopic or surgical feeding jejunostomies are aimed to prevent a future surgery for intestinal feeding access. Mainly performed during any abdominal surgeries with no current and clear indication for intestinal feeding, such as a pancreaticoduodenectomy	[21–23]
Miscellaneous	Permanent access for ERCP	To access to biliary tract for endoscopic procedures a subcutaneous blind isolated loop of jejunum is constructed after a roux-Y hepaticojejunostomy	[24, 25]
	Intestinal auto-transplantation		[26]

Surgical procedures for primary prophylactic surgeries may include abdominal or inguinal hernia repairs, intestinal resections, endoscopic or surgical drainage of a duplication, an abscess or a cyst, endoscopic or surgical removal of a polyp, closure of an omental or mesenteric openings after a major abdominal surgery. Types, surgical procedures, and aims or rationale for prophylaxis have been reviewed in Table 16.1.

16.3.1 Primary Prophylactic Surgeries for Small Intestines

16.3.1.1 Prophylactic Hernia Repair

Abdominal wall hernias are common in our daily surgical practice. As an historical viewpoint, diagnostic criteria and indications for hernia surgery are clearly defined and surgical procedures are refined and nearly standardized. Inguinal hernias are common but incisional hernias also require clinical and surgical endeavor to manage hernia related complications and clinical outcomes. Almeflh et al. (2019) have studied asymptomatic umbilical hernias in pediatric group [3]. In their systematic review, they have concluded that asymptomatic and uncomplicated umbilical hernias may be conservatively managed till 4–5 years of age. Prophylactic umbilical hernia repair may be considered after these ages, when overall risk is acceptable for surgery [27]. Gong et al. (2018) have recently reported that watchful waiting for asymptomatic or minimally symptomatic inguinal hernias may merely delay the need for surgery [2]. Thus, even in asymptomatic inguinal hernias, prophylactic hernia repair may be considered to prevent future inguinal hernia related intestinal obstruction and strangulation [28, 29]. Further guidance may be available from international guidelines for inguinal hernia management [30].

16.3.1.2 Prophylactic Intestinal Resections

Meckel's diverticulum (MD) is a congenital malformation and related with life-time risk of complications [31]. Most of MD remain incidental and may be related with gastrointestinal bleeding, intestinal obstruction, and inflammation. However, preoperative diagnosis has limitations with imaging and requires laparotomy or laparoscopy. Complication related risk factors are reported to be gender (male), age (younger than 40), size of diverticulum (longer than 2 cm), and macroscopic mucosal alterations observed during surgery. Segmental resection and anastomosis are the recommended procedure to minimize residual heterotopic mucosa. McKay (2007) has reported results of 29 cases with MD in 2007. Ratio of symptomatic cases to asymptomatic cases was 9/20. Male to female ratio was 16/13. Symptomatic cases were significantly younger than the asymptomatic cases (Mean ± SD ages were 34.9 ± 23.2 years compared with 64.2 ± 16.5, respectively). Twenty cases with MD were treated with surgery and 10 of these cases were asymptomatic. Laparoscopic segmental resections and diverticulectomies were performed and these surgical procedures were not comparable for postoperative complications and results. In addition, heterotopic mucosa was not observed in the asymptomatic MD cases [32].

Pariza et al. (2011) have reported their experience with 62 MD cases [33]. Thirty MD cases were incidental; male gender and younger age were significantly related with symptomatic and complications in their series. They have reported two cases of diverticulum tumor, an intussusception case, and a perforation case with unknown object. Post-diverticulectomy complications were not rare (1 in every 4 cases have been reported to have complications) and suppuration was the most common. Blouhos et al. (2018) have reviewed surgical concerns on MD in adults in 2018 [34]. They have not recommended routine resection in asymptomatic MD cases and listed some risk factors for developing future complications to be considered before surgery These risk factors included patient age (younger than 50 years), gender (male), diverticulum length (longer than 2 cm), and presence of ectopic or abnormal features within the diverticulum. They have recommended diverticulectomy for long and wedge resection for short MD. Mora-Guzman et al. (2018) have updated their series in 2018 with 66 cases [35]. In this recent report, they have observed three cases of neuroendocrine tumors. To summarize, male and young patients (younger than 40 age) with incidental MD may be considered for routine prophylactic segmental resection. For all cases with incidental MD between 40 and 50 years of age, prophylactic surgery should be considered on case by case conditions and risk factors. There is no specific need of prophylactic surgery for female gender with incidental MD. However, for all cases with incidental MD patients older than 50 should not be considered for routine prophylactic surgery for incidental MD.

16.3.1.3 Endoscopic or Surgical Drainage

Small intestinal duplication cysts are rare clinical entities and are commonly observed in jejunum and ileum. Duodenal duplication cysts are relatively observed less frequently [36]. Duplication cysts are located on the mesenteric side of gastrointestinal tract but have no luminal openings. These cysts may contain any heterotopic mucosa and have a muscular wall, with the same vascular supply with the intestinal segment, which the cysts have been adjacently located [37, 38]. Duodenal duplication cysts are commonly located in the second and the third portion of the duodenum and may be related with pancreaticobiliary system [11, 36]. Gastrointestinal duplication cysts are developmental abnormalities, and common in the newborn and early childhood. However, cases after twenties have been reported. There is no male or female selection in demographic features [11]. Clinically small intestinal duplication cysts may present with mild symptoms and may be defined with imaging studies. However, gastrointestinal bleeding, intestinal or biliary obstruction, and pancreatitis may complicate the clinical course [39]. Heterotopic mucosa was previously mentioned, and carcinoids or adenocarcinoma has been related to duodenal duplication cysts [40, 41]. A small intestinal

duplication cyst with symptoms or complications merits a surgical intervention. Minimal invasive surgery with endoscopy or laparoscopy may be considered, and the prognosis is expected to be fair [36]. With the use of computed tomography and ultrasound may catch a small intestinal duplication cyst [42]. In such situation a prophylactic surgery may be rational approach, rather than watch and wait. Simple drainage, total or partial cystectomy, cyst fenestration or resections may be considered on case by case basis accordingly [43].

16.3.1.4 Endoscopic or Surgical Polypectomy

Small intestinal polyps or polyposis may not be common, but duodenum is the primary site. Gaspar et al. (2016) have outlined endoscopic interventions for both benign and precancerous duodenal lesions [44]. Endoscopic or surgical interventions may be indicated or considered during a surveillance of a patient with polyposis [13, 14].

16.3.1.5 Closure of Omental or Mesenteric Openings

After a major abdominal surgery which includes a gastric resection, a pancreaticoduodenectomy or a transvers colon resection, or during gastric bypass surgery a potential defect in gastrocolic ligament, omentum, or mesentery has been created. A potential intraperitoneal defect is known to be related with internal herniation, small intestinal obstruction, and strangulation [15, 16]. Thus, whenever an internal defect is created a prophylactic closure should be performed to minimize the risk of internal herniation related complications.

16.3.2 Secondary Prophylactic Surgeries with Small Intestines

16.3.2.1 Prophylactic Stoma Formations with Small Intestine

Total colectomy with ileorectal anastomosis or total proctocolectomy with ileoanal anastomosis is performed to treat colorectal polyposis or inflammatory bowel disease. To prevent ileorectal or ileoanal anastomosis, a proximal stoma formation with temporary ileostomy may be constructed. In such cases, primary intentions will be to decompress distal anastomosis, to minimize anastomotic leakage, and to decrease ileorectal or ileoanal fistula rates and intrapelvic or intra-abdominal sepsis. Recently, Güenaga et al. (2008) have reviewed five randomized clinical trials for temporary use of ileostomy or colostomy (68 and 166 in each group, respectively) for colorectal anastomosis [45]. The primary end points were "mortality, wound infection, time of stoma formation, time of stoma closure, time interval between stoma formation and closure, stoma prolapse, stoma retraction, parastomal hernia, parastomal fistula, stenosis, necrosis, skin irritation, ileus, bowel leakage, reoperation, patient adaptation, length of hospital stay, colorectal anastomotic dehiscence, incisional hernia, and postoperative bowel obstruction." They have concluded that only stoma prolapse was significant. For practical reasons, prophylactic ileostomy may be considered after a colorectal anastomosis formation. However, Gavriilidis et al. (2019) have concluded that an ileostomy is not favored when stoma formation and closure related complications have been considered [46]. Chudner et al. (2019) have suggested decreases morbidity rates with loop ileostomy after anterior resection in the expense of dehydration risk [47]. In this study, 666 LI and 397 LC were compared, a data which may reflect the surgical practice.

16.3.2.2 Feeding Jejunostomy

Nutritional supplement may be essential after a major abdominal surgery. Whenever possible oral or enteral route is preferred. A temporary supplement may be required to oral intake with a feeding jejunostomy [21–23]. Esophagus and gastric cancers are known to deplete the patient nutritionally. After restoration of gastrointestinal continuity, it may take time to begin oral intake, or additional supplement may be needed. Feeding jejunostomy may be constructed during the initial surgery or an endoscopic placement of feeding catheter may be the other option.

16.3.2.3 Permanent Access for ERCP

Hepaticojejunostomy may be performed after a biliary resection for benign or malign disorders

such as strictures, extrahepatic biliary lesions, or periampullary mass. Reconstruction of hepaticojejunostomy may limit the access to biliary tract through the upper gastrointestinal tract. Thus, a formation of a permanent access has been reported to help in such conditions to biliary tract. This access is achieved with subcutaneous blind isolated loop of jejunum, which is constructed after a Roux-Y hepaticojejunostomy [24, 25]. There is limited data for the outcomes, but when a route to biliary tract through upper gastrointestinal tract with an endoscope, this procedure may be considered.

16.3.3 Intestinal Auto-Transplantation

Small intestinal transplantation has not been reported previously as a prophylactic surgery. It will not be a routine, but to outline the rationale of prophylactic surgery a case of intestinal auto-transplantation will be discussed in this section. Cheng et al. (2018) have recently reported an ex vivo resection and intestinal autotransplantation [26]. The procedure was required for a desmoid tumor removal in a patient with familial polyposis. In this case, resection was complicated due to vascular involvement. However, a preemptive resection of the superior mesenteric artery shed area was planned. Surgery was completed with resection, and autotransplantation was performed with jejunostomy. As to say, prophylaxis may sometime require do more now rather than tomorrow, and another sometime do less now, and wait.

16.4 Role of Minimal Access or Invasive Surgery in Prophylactic Surgery of Small Intestines

Abdominal surgery is a major risk factor for the development of postoperative ileus, obstruction development, and abdominal wall hernias [48]. However, minimal access or invasive surgery techniques may be indicated, accessible, and considerable whenever possible. Some examples may include a percutaneous drainage of an abdominal cyst or abscess with ultrasonography guidance, which may exclude an abdominal surgery completely [49]. Using laparoscopy or robotics to resect a colorectal cancer has clear advantageous over open surgery to minimize surgical complications which may affect small intestines [50]. Endoscopic removal of precancerous polyps or endoscopic mucosal resections of early gastrointestinal cancers may have the same effects to minimize risk of abdominal surgeries [51]. This section has outlined the need of the consideration of the surgical technology as a mean of prophylactic approach to prevent small intestinal anatomical and functional integrity. We the authors strongly recommend a minimal access or invasive surgery, whenever feasible and accessible for abdominal procedures. This approach may prevent small intestines from surgical complications such as intra-abdominal adhesions or abdominal wall hernias and related intestinal complications mainly intestinal obstructions, strangulations, and intestinal resections.

16.5 Conclusion

Prophylactic surgery of small intestines is primarily needed whenever a clear risk of anatomic or functional loss of small intestine. This risk may arise from an inflammation which may cause bleeding, obstruction, and perforation. These conditions may require advanced and emergent interventions such as further intestinal resections related with severe intestinal insufficiency. Even fatality may occur. In some certain clinical precancerous lesions, prophylactic resection of lesion may be considered.

Small intestinal surgeries may be needed with the intent of other prophylactic aims or rationales. In these conditions, the aim or rationale of small intestinal surgical procedures is not related to prevent small intestinal functions or anatomical integrity. These procedures include loop ileostomy to decompress a distal anastomosis, a preemptive feeding jejunostomy after a major abdominal surgery, a construction of a blind subcutaneous jejunal loop to access a biliary anastomosis.

Prophylactic small intestinal surgeries may be performed with endoscopic, laparoscopic (even with robotic), or open surgical techniques. Hernia repair, resections, construction of a stoma, lysis of adhesion, and even an auto-transplantation may be indicated or considered as a prophylactic procedure. Minimal access or invasive surgery may minimize future intestinal adhesions which are known with risk of intestinal obstructions.

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Prophylactic Appendectomy

17

Osman Nuri Dilek, Haldun Kar, and Turan Acar

17.1 Introduction

Appendectomy is one of the most performed abdominal operations. It is an operation performed for 285 years since Claudius Amyand performed the first appendectomy in 1735. The frequency of appendectomy has been reported between 75–135/100,000 per year [1]. It is reported that the rate of appendicitis diagnosis has increased by 0.5/100,000 annually since 1995 [1, 2]. The incidence of appendicitis may differ according to age, sex, race, and socioeconomic status. It is slightly more common in men, and the male/female ratio has been reported as 1.08 [1]. The diagnosis of appendicitis varies periodically and is most often made in the third quarter of the year in the summer [1]. The accuracy of the diagnosis of appendicitis varies depending on gender, and the correct rate of diagnosis in women (78.6%) is lower than the rate of correct diagnosis in men (91.2%) [3]. An epidemiological study conducted in South Korea calculated that 16% of people were diagnosed with appendicitis at some point in their lives, and 59.7% of whom underwent appendectomy. It has also been stated that the reason for the appendectomy rate in South Korea to be higher than western societies may be due to the National Life Insurance, whose scope has been extended in recent years [1].

Appendicitis was found most frequently in the 10–14 age group in males and the 15–19 age group (169/100,000) in females, while it was the least (36/100,000) in the group under 5 [1, 2]. In 75–79 age group, in which appendicitis is also common, complications have been encountered more frequently.

In the literature, peaking in 10–19 and 74–79 age groups is defined as an M-shaped pattern [1, 4, 5]. Anderson et al. (2012) reported that the frequency of lifetime appendicitis varies with age [2]. According to this study, it was calculated as 3.2% in 20 age group, 5.5% in 40 age group, 7.2% in 60 age group, and 9% in group above 85 years old [2]. In America, the rates are different, and 12% of men and 23% of women have been found to have an appendectomy. Whites and Hispanics were diagnosed with appendicitis more, while those with African and Asian origins were diagnosed less. Also, the rate of diagnosis of appendicitis was higher, and the rate of perforated appendicitis was lower in those with comprehensive health insurance [2, 3, 6]. It is also

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known that the risk of appendicitis is lower in communities fed a fiber-rich diet [1, 7].

In the literature, 20–30% of cases in appendicitis series are perforated appendicitis, and in epidemiological studies, the incidence of perforated appendicitis was found to be 29/100,000 [1, 2]. The risk of perforation is slightly less in women. The perforation risk is higher in the oldest (≥85 age) and youngest (0–4 age) patient group. Perforation was detected in 15.4% of the cases in the 15–19 age group and 52–55% of the patients over 85 years old [1]. Interestingly, it was found that perforation was more common in Hispanics and Asians and people without private insurance [2]. The period with the highest frequency of perforation was determined as winter months (December). The rate of cases with perforated appendicitis detected in a particular hospital has decreased over time due to increased teamwork [2].

17.2 Approach to Appendix Problems

17.2.1 Nonsurgical Approach for Appendicitis

There are some clinical studies on the medical treatment of appendicitis. Studies are stating that up to 90% of successful answers have been obtained with antibiotic treatment, especially in appendicitis series selected without complications [8, 9]. Hansson et al. (2009) reported that antibiotic therapy was successful in 92.2% of cases with antibiotic therapy in their series of unselected patients. However, 13.9% of cases developed recurrent appendicitis, and major complications were seen three times more in the appendectomy group [10]. In general, the preference of surgeons for appendicitis still favors appendectomy.

17.2.2 Protection of the Appendix

Some authors think that the protection of the appendix will be beneficial. "Appendiceal conduits" can be used in the treatment of some urological, neurological, and biliary pathologies. The appendix has been used for the purpose of eliminating fecal incontinence in Spina bifida, Hirschsprung's disease, imperforate anus, and some neurological diseases (MACE procedure), for biliary reconstruction in choledochal cysts, and appendico-vesicostomies (Mitrofanoff procedure) [11]. In the literature, such studies are very few and usually in the form of a case report. However, the use of the appendix for reconstruction has diminished due to the development of surgical and minimally invasive techniques. However, some suggest that the appendix be preserved due to the possibility of using it for "tubular conduit" in the future [12].

17.3 Appendectomies

The appendectomy procedure is simple and technically well-standardized surgery. Appendectomy is performed during many procedures without questioning whether there is an infection/pathology. In the last 20 years, the appendectomy rate has started to increase with the laparoscopic approach due to less pain, more comfort, shorter hospitalization, shorter postoperative ileus, and low risk of infection, and today 74.6% of cases are performed laparoscopically. This rate is slightly lower (63.3%) in perforated appendicitis [2, 13, 14].

There is no consensus about the normal appendix in laparotomies. Especially in cases of endoluminal appendicitis, it becomes more challenging to diagnose. Some authors suggest performing an appendectomy, even if the appendix is normal-looking, in the lower right quadrant pain, the reason for which cannot be understood [2, 13, 15]. On the other hand, most of the authors recommend performing prophylactic appendectomies before 30 years of age [14].

Appendectomies, which are the valid treatment in the treatment of acute appendicitis in the clinic, have also clinical applications in the form of prophylactic, incidental, and interval appendectomy (Table 17.1). All three applications are for prophylactic purposes.

Table 17.1 Classification of etiologic factors for prophylactic appendectomy

Prophylactic appendectomy		Incidental appendectomy	
• Appendiceal masses	• Metal intoxication (Hg)	• Mesenteric lymphadenitis	• Emergency sigmoidectomy
• Diveticular disease	• FMF	• Urinary diversion	• Bariatric surgery
• Space travel	• Fecalith (Appendicolith)	• Omental tortion/ infarction	• Abdominal cocoon syndrome
• Pole travel	• Plastrone (interval)	• Crohn's disease	• Negative laparotomy
• Foreign bodies		• Radical cystectomy	• Amyand hernia
• Parasites	• Baryum meal	• Ovarian pathologies	• Cesarean
		• Cytoreductive surgery	• Incisional hernia repair
	• Malrotations		• Intussusception
	• Chronic pelvic pain		• Cystic fibrosis
	• Right colon diverticula		• VP shunts for hydrocephalus
	• Endometriosis		

FMF Familial mediteranean fever, *VP* ventriculoperitoneal, *Hg* Mercury

17.3.1 Incidental Appendectomy

Incidental appendectomy (IA) can be defined as adding an appendectomy to the procedure while performing another surgery. It is performed to prevent appendicitis complications, probable difficulties in differential diagnosis, and a second surgery in the future. The current incision is used for appendectomy [14]. In 1902, Kelly surveyed 80 well-known surgeons on the IA. Thirty seven percent of surgeons reported that they routinely perform IA, and 72% reported that they performed an appendectomy if the appendix was attached to the surrounding tissues [3, 16]. Kelly, who opposes IA, published this survey and its results in JAMA in 1902, as the function of the appendix is not yet known and will increase surgical morbidity. Appendectomy for reasons other than appendicitis has been discussed in the literature for a long time. Inversion appendectomy, defined in 1895 and popularized in the 1960s for a short time, aimed to reduce the risk of infection and congestion. It was abandoned due to impaired blood supply of the appendix and increased risk of necrosis and intussusception. However, some series reporting that PA performed by the invagination method during cesarean does not negatively affect mortality and morbidity [17]. The interval appendectomy is another form of PA, which is performed in months after the regression of plastron appendicitis. Interestingly, 69% of patients undergoing appendectomy for acute appendicitis are under 30 years of age, while 75% of patients performed IA are over 25 years of age [3, 18].

Snyder et al. (1998) reported the lifetime IA rate as 2.9% in men and 16% in women. In male patients, 36.6% of cases were reported to be performed during cholecystectomies, 11.8% of bowel resections, and 4.9% during hernia operations [3]. In female patients, 45% of incidental appendectomies were performed during hysterectomies, 37.5% during salpingo-oophorectomy, 18.4% during cholecystectomy, and 7.2% during oophorectomy. IA is performed more (6–12 times) during gynecological operations, especially of women of reproductive age [3]. They recommended to add appendectomy to women under 35 years of age during gynecological interventions. There is no consensus in 35–50 years old patients due to the risks associated with appendectomy (bleeding, infection, ileus, increased morbidity rates). It is not generally recommended over the age of 50 [3]. As the gynecological surgeries started to be performed more laparoscopically, incidental appendectomies were also started to be performed more. In common gynecological pathologies such as endometriosis, ovarian cyst torsions, and cyst ruptures, the laparoscopic approach is preferred and many gynecologists add IA to the procedure. Apart from these, the appendix was also removed during laparotomies for different reasons (Table 17.1).

Appendectomy is frequently added to the procedure in cases where laparoscopy is performed to determine the ***chronic pelvic pain*** etiology. On the other hand, the probability of negative appendectomy increases 2.5 times in women of childbearing age due to pelvic pathologies [3, 18]. Different results have been reported in the evaluation of the specimens whose histopathological examination was performed to clarify the etiology of pelvic pain. Krone et al. (1989) reported that 1718 (32%) appendectomy performed in the series of 5369 gynecologic laparotomy cases. In the histopathological evaluation of appendectomy specimens, appendix was found to be morphologically normal in 368 (21.4%) cases, acute appendicitis in 136 (7.9%) cases, and chronic appendicitis in 1118 (65.1%) cases, and carcinoid, mucocele and endometriosis in 96 (5.6%) cases [19].

Endometriosis syndromes also play an important role in the etiology of chronic pelvic pain. The coexistence of endometriosis in the appendix varies according to the selected patient group. Although endometriosis is rare (0.2%) in patients with acute appendicitis, the frequency of endometriosis varies between 9.3% and 39% in the appendix of patients with endometriosis syndrome. The rate of endometriosis in the appendix of patients with reproductive pelvic pain has been reported as 8.5% [18]. Appendix pathology is detected in 30.2–59.0% of patients in this group. Interestingly, the incidence of carcinoid tumors in the appendix in the population was 0.3–1.0%, while this rate was reported as 2.3–4.2% in women of reproductive age [20]. In cases of deep infiltrative endometriosis (DIE), the risk of endometriosis in the appendix is further increased (15.5–39.0%) [21]. IA to be performed in these patients may have an important contribution in eliminating possible appendix pathologies and pelvic pain. Lynch et al. (1997) reported that pelvic pain resolved in 117 (90%) of 130 cases they performed appendectomy for pelvic pain [22]. Appendectomy can be performed synchronously during the gynecological intervention as well as prophylactically in cases with subsequent diagnosis of endometriosis [18]. As a result, in one of 10 patients with endometriosis, one in 4 patients with DIE, IA disease will be a preventive procedure.

There are many publications stating that appendectomy has been added to the process during ***malrotations*** (Fig. 17.1), atresia, intussusception, ovarian torsion, mesenteric lymphadenitis, incisional hernia repair, and colon resections [13, 23]. In patients undergoing Ladd's procedure due

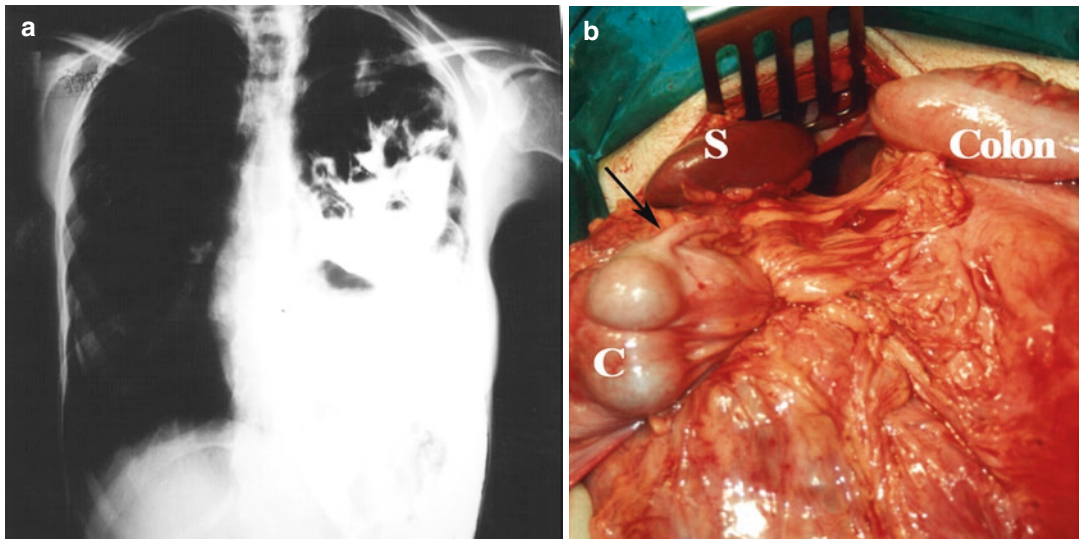

Fig. 17.1 This picture (**a**) shows the case in which we underwent an appendectomy (arrow) from the left thoracotomy (**b**) in a patient with intestinal malrotation and Bochdalek hernia. *S* spleen, *C* caecum (Archive of ON Dilek)

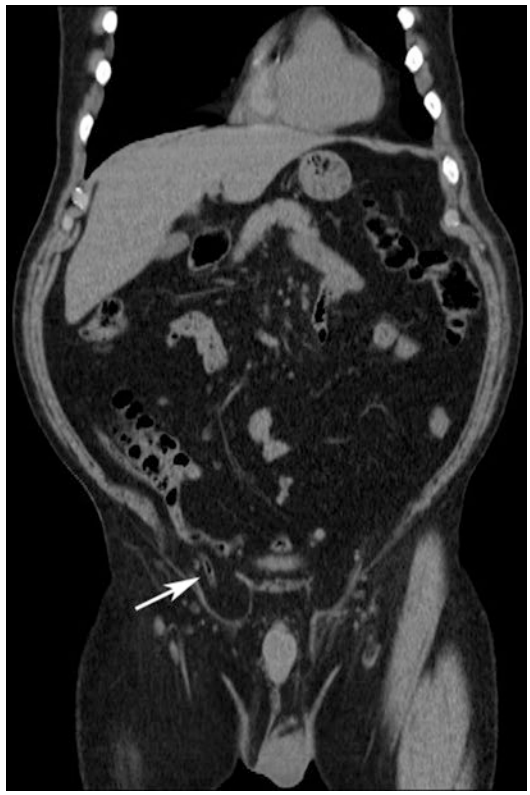

Fig. 17.2 Amyand hernia (arrow) is seen in the CT coronal section

to intestinal malrotation, IA is added to the procedure.

Some authors suggest appendectomy in cases with appendix (De Garengeot hernia) in the inguinal ***hernia*** sac (Amyand hernia, Fig. 17.2) or the femoral hernia sac during inguinal hernia surgery [24]. IA is also performed during hernia surgeries. Dens adhesions occur after the wide abdominal defects are covered with mesh, and it may makes difficult for subsequent surgical entries. Dilek et al. considering that the intense fibrosis that will occur after mesh applications for the repair of giant incisional hernia would make subsequent operations difficult, they performed IA in 23 incisional hernia cases in their series of 64 IA (2001) cases [25]. However, some authors do not recommend appendectomy especially in cases with mesh application and in cases with normal appendix [26].

There are some studies that incidental appendectomies are performed in addition to laparoscopic cholecystectomy, bariatric surgery, cardiac surgery, urological procedures, trauma surgery, and transplantation [14, 27, 28]. While there are authors that encourage appendectomy during bariatric procedures for obesity, there are also those who do not recommend it in cases where it is difficult to dissect the appendix in super obese [29]. Akbulut et al. (2020) reported that they did 170 incidental appendectomies in 1910 cases performing living donor hepatectomy, as a result of histopathological examination, they found normal appendix in 137 cases, fibrotic changes in 13 cases, acute appendicitis in 6 cases, *Enterobius vermicularis* in 5 cases, lymphoid hyperplasia in 4 cases, and various types of neoplasia in 7 cases. They also concluded that inspecting the appendix and seeking morphological changes could contribute to making an appendectomy [30].

The appendix is often removed during oncological surgery. In patients with Wilms tumor, appendectomy is performed together with nephrectomy. Especially in pediatric oncology cases, it is recommended to remove the appendix during surgery due to the risk of developing an acute abdomen due to chemotherapy and neutropenic enterocolitis [12]. However, IA is not recommended for patients with severe comorbidity, using immunosuppressants, vascular grafts and over 60 years of age [3, 25].

It has been reported in many studies that incidental appendectomies have no negative effects on perioperative ***morbidity and mortality***. It was reported that there was no significant difference in morbidity after inguinal hernia surgery, incisional hernia, and hysterectomy operations [13, 19, 31, 32]. While there was no significant difference between Pollock and Evans's series that underwent laparotomy, cholecystectomy, and IA, and antibiotics were used, the risk of infection was found to be higher in the series that did not use antibiotics [33]. However, there are also series that undergo laparoscopic cholecystectomy and IA and report that there is no significant difference [34]. Strom et al. (1983) found that incidental appendectomies in patients undergoing laparotomy due to trauma and without surgical pathology significantly increased morbidity. In another prospective study of the same author

and colleagues, they reported that there was no significant difference in morbidity between the appendectomy group and the non-appendectomy group during the laparotomy [28]. Morris et al. (1987) reported that 210 patients who underwent laparotomy due to Hodgkin's disease, IA were added to procedure in 130 patients and there was no significant difference in terms of morbidity. On the other hand, there are also publications reporting that the addition of IA prolongs wound infection and hospital stay while performing laparoscopic cholecystectomy [35].

There is a general opinion that IA prevents future appendicitis and complications. In many epidemiological studies in the literature, it has been reported that 20–25 IA prevents one future appendicitis and its possible complications [1, 3]. In the literature, abnormal pathological findings were found in 16–73% of the cases in histopathological examination of the patients who were considered to have normal appendix during laparotomy [3, 13, 36]. With the IA, as expressed in the Turkish statement of "*shooting two birds with one stone*" the patient will be free from two problems: single anesthesia, single hospitalization, one laparotomy, and the risk of appendicitis in the future and associated complications.

17.3.2 Prophylactic Appendectomy

Prophylactic appendectomy (PA) can be defined as the removal of the appendix without any further action. Indications and risks should be determined in patients for PA. Decisions should be made by talking to the patient or relatives for diagnosis and surgery. Morbidity and mortality are undesirable. PA is performed for many reasons (Table 17.1).

Fecalith or ***appendicolith*** formed within the appendix are among the most common causes of appendicitis (Fig. 17.3). In clinical studies, the risk of recurrence of appendicitis has been reported to be 72% in patients with appendicolith. Interval appendectomy is recommended for patients who previously had attacks due to fecalith or appendicolith [37]. In the retrospective computed tomography scan of 2913 patients of

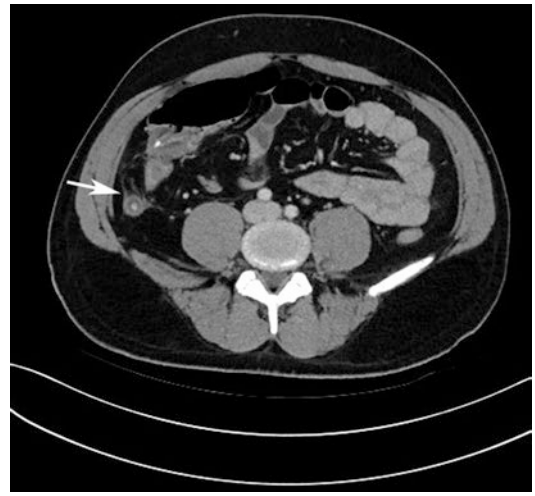

Fig. 17.3 Fecalitis is seen (Arrow) in the appendix

18 years or younger of age, Rollins et al. (2010) revealed appendicoliths in 75 cases (2.6%) [38].

Appendix ***foreign bodies*** are very rare entities. Peristaltic strength of the appendix may not be enough to push foreign bodies into the cecum. Metal and similar objects more massive than the gravity of the appendix content settle in the channel. However, foreign bodies rarely (0.0005%) can cause appendicitis [39]. Foreign bodies rarely show symptoms, and most are detected by chance during examinations. There is no need to remove foreign bodies in the appendix routinely. However, long, thin, and sharp-edged foreign bodies should be initially removed endoscopically. In cases that cannot be removed, PA should be recommended [40]. There are also authors suggesting routine appendectomy on foreign bodies detected in young children [41]. In cases where mercury taken with mercury poisoning accumulates in the appendix, symptoms of chronic poisoning may be encountered. In the case of mercury poisoning, a medical and endoscopic approach can be treated as well as authors are recommending PA [42]. It has been reported that the barium meal used during radiological examinations may accumulate in the appendix and cause appendicitis. Patients undergoing such radiological procedures should be informed that appendicitis and PA are recommended in symptomatic patients [43].

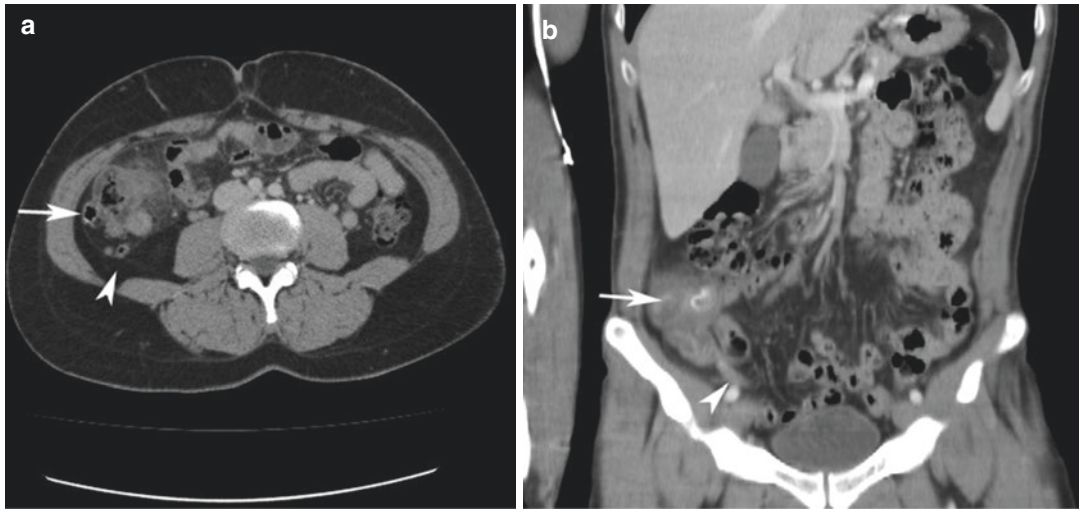

Fig. 17.4 Normal (**a**) and complicated (**b**) cecum diverticulum (arrow) and normal appendix (arrowhead) are seen in two different patients' abdominal CT images

Although appendix ***diverticulum*** is very rare, PA is recommended in clinical series due to the risk of malignancy ranging from 7.1 to 47.8% and high risk of confusion with mucocele (9.8%–33%) [44–46]. Right colon diverticula often confuse clinically with appendicitis (Fig. 17.4). Abdominal tomography is useful in the differential diagnosis. In the right colon diverticulitis series of 113 cases of Yang et al. (2008), 56 patients were diagnosed correctly, and medical treatment was performed, while 51 patients were operated with the diagnosis of acute appendicitis. There are also studies suggesting PA after medical treatment in patients diagnosed with right colon diverticulitis [47].

In recent years, the removal of ***luminal pathologies*** endoscopically and by the mucosal resection has started to be made increasingly. In such a case, we performed PA in a patient with edema and inflammation in the appendix due to the clips placed on the control computed tomographies taken after the EMR performed close to the appendix radix (Fig. 17.5).

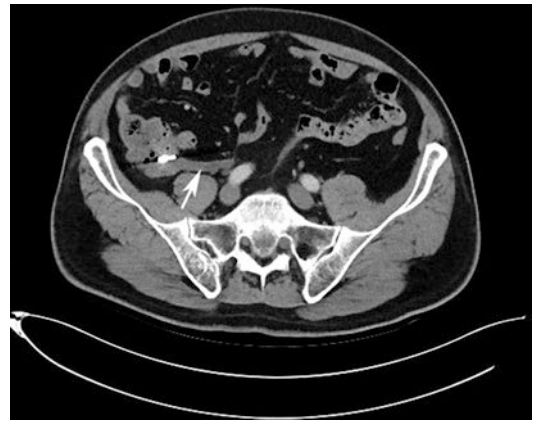

Fig. 17.5 The abdominal CT axial section shows the clips in the radix and congested appendix (arrow) of our patient who underwent endoscopic resection for the lesion in the cecum

There are many studies on whether the ***parasites*** cause appendicitis in the appendix. The most common parasites found in the appendix are helminths (*Enterobius vermicularis, Schistosoma spp, Taenia spp, Trichuris trichiura*, and *Ascaris lumbricoides*) and protozoa (*Entamoeba histolytica, Balantidium coli*, and *Cryptosporidium parvum*). The parasites are thought to cause appendicitis by blocking the lumen, leading to lymphoid hyperplasia or inflammation. The frequency of parasites in the appendix varies depending on the countries' socioeconomic levels and eating habits. Parasites were detected in 0.5% of cases in a study from Hong Kong, 5.5% of cases in Oman, and 16% of

cases in Malaysia [48, 49]. The most common parasite in the appendix is *Enterobius vermicularis*, and its incidence has been reported between 0.2% and 41.8% (average 4.5%) [50, 51]. The incidence of appendicitis in appendixes with parasites is very different in clinical series. In the literature, Zakaria et al. (2013) reported the appendicitis rate as 5.5% of their 1600 cases series. It was reported as 14.6% in Hong Kong series, 42.5% in Malaysia, and 81.3% in Pasupati series [48–50]. It has been reported in many series that the incidence of parasites in the lumen of the appendix and the risk of appendicitis is very low, and the main cause of appendicitis is not. There is no consensus on performing PA due to the presence of parasites in the appendix. Anti-parasitic therapy should be initiated in those with or without appendectomy.

17.4 Miscellaneous Conditions

Chronic appendicitis *is an entity characterized by chronic inflammation in the appendix wall, which is shown as the cause of chronic abdominal pain in the clinic.* Occasionally, an acute abdomen was held responsible for intestinal obstruction and perforations [52]. However, due to the difficulties in its diagnosis, it can be accepted as an entity that has not been consensus. It is frequently encountered as a histopathological diagnosis in prophylactic appendectomy series in the clinic. In their series of 748 cases by Schumacher and Schwartz (1986), they reported chronic appendicitis in 27% of cases and normal appendix in 73% [36]. In another PA series, appendectomy was performed due to chronic pelvic pain in 15 cases, and their histopathological analysis demonstrated that chronic appendicitis in 4 cases, malignancy in one case, acute appendicitis in one case, and normal appendix in 9 cases [13]. In 269 cases of appendectomy series of Leardi et al., chronic appendicitis was diagnosed in 38 cases (14.2%). In their postoperative follow-up, they observed that 33 of the patients' abdominal pain disappeared. They concluded that chronic appendicitis might have a role in recurrent abdominal pain, and PA may be effective [53].

Plastron appendicitis may occur when the omentum surrounds the appendix in cases of appendicitis that progresses towards the perforation and abscess formation. As a complication of appendicitis, more than 90% of cases improve with medical treatment and drainage performed in plastron appendicitis cases. Acute appendicitis recurs again in 5–26% of the recovered cases. While the risk of recurrence of appendicitis increases in the first 6 months, it decreases after the first year. In such cases, two approaches are recommended. Mentula et al. (2015) recommend surgery in the early period (acute phase) as a fewer follow-up, fewer hospital admissions, fewer patients are admitted, and fewer interventional procedures will be performed [54]. There is also more risk of malignant neoplasia in 0.7% to 3% of patients with plastron appendicitis, and the risk of malignancy is higher than 40 years of age. In the early stages, this risk can be eliminated with therapeutic appendectomy [55–58]. A group of authors suggests that the medical approach should be preferred in the early period, and the interval appendectomy should be performed after 3 months because it contains fewer complications. It is also recommended to perform MRI before surgery [55, 57]. Besides, some authors stated that follow-up with MRI would be sufficient.

There are some speculations and many research about ***the increased risk of cancer*** in patients who have undergone appendectomy in the past, and their relationship with cancer has not been found [3]. However, in a retrospective cohort study with broad participation from Taiwan in recent years, it has been reported that developing colon cancer is 1.14 times higher in people who underwent an appendectomy and followed for 14 years (12.8 times). In the same study, they reported that the risk of developing colorectal cancer is much higher in the follow-up of patients undergoing an IA. Interestingly, it is known that a colon carcinoma should take about 10 years to develop from a polypoid lesion; this period was found between 1.5 and 3.5 years postoperatively

after appendectomy [59]. Age-related changes in the intestinal flora and the immune system are known to be weakened due to age, and there is insufficient clinical data on the relationship of the event to appendectomy. It is known that genetic, nutritional, and environmental factors play an important role in the development of colon cancer. Prospective clinical studies with broad participation are needed to reveal the relationship between appendectomy and colorectal cancer.

Although the appendix is thought to play a role in the ***immune system*** due to its lymphoid tissue content, there is insufficient data on the negative effect of appendectomy on the immune system and homeostasis [60]. There are also studies on the natural and dense microbiota in the appendix, which is a "*safe house*," that it plays an important role in the regulation of the flora (microbiota and biofilm) in the colon, and changes occur in the colon flora after appendectomy [61]. In the literature, there are studies reported that the risk of developing Crohn's disease increases 1.6–2.1 times in individuals who underwent appendectomy, or a decrease in the incidence of inflammatory bowel diseases, especially ulcerative colitis [2, 62]. There are even studies reporting that patients with ulcerative colitis have decreased immunosuppressive medication needs, and relapses and symptoms decrease after appendectomy. However, all these data need to be investigated with large prospective series [63]. While there are more than 500 types of bacteria in the intestines, studies are reporting that there are genomic links between Fusobacterium nucleatum/necrophorum found in most acute appendicitis and the development of inflammatory bowel disease and subsequent colorectal cancer [12, 64].

There are many studies on whether PA is ***cost-effective*** or not. In studies conducted, it has been reported that incidental appendectomies and prophylactic appendectomies performed before the age of 30 have a positive and cost-effective contribution [65]. The operation must be performed with minimal complications. Twenty years after a PA, a case with ileus and intestinal necrosis due to regional adhesions has been reported in the literature [14].

17.5 Conclusion

Prophylactic or incidental appendectomy can ethically be performed with minor complications. PA should be recommended in patients without comorbidity and at a younger age (<30). IA should be performed in patients who are considered to have no adverse effects on morbidity and mortality and thought that IA would be beneficial. The surgery decision must be made with the patient and family. In addition to preventing future appendicitis and associated complications, PA will also assist in the early diagnosis of appendix malignancies.

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18 Vascular Problems Related to Colectomy: Habitual and Variant Anatomy, Prevention, and Tactical Aspects

Abe Fingerhut, Hayato Kurihara, and William Tzu-Liang Chen

18.1 Introduction

While the normal vascular anatomy of the colon and rectum is well documented [1, 2], variations are highly prevalent and may be an underlying cause of vascular failure after colonic resection and anastomosis. Indeed, adequate oxygen supply is mandatory for the normal healing process [3–5]. Insufficient blood supply, with its obvious corollary, insufficient oxygen supply to the site of healing (anastomosis), and thus a risk factor for anastomotic breakdown, can be secondary to inadvertent division (whether the vessel is in its "normal" situation, or not), stretching or twisting of the alimentary vessels of one of the enteric segments, or division of vessels as necessary to perform a procedure (high or low tie of the inferior mesenteric artery with its corollar interruption of the left colic artery), especially when there is an insufficient anastomotic arc between the superior and inferior mesenteric circulations at the level of the marginal artery (of Drummond) or Griffiths' point, absence of the middle colic artery (MCA) or one of its branches, and last, but not least, when vascular supply to the colon does not take its normal course, notably when atherosclerosis or previous colectomy obstructs or interrupts the normal vascularization.

Moreover, several anatomic regions along the gastrointestinal tract are known to have a tenuous vascular supply and after dissection and division of adjacent vessels, the gastrointestinal segment can become hypo-perfused, or even ischemic. This is the case when small hypoplastic vessels are present, notably at the level of Griffiths' point [6]. Ischemia of the intestinal segment to be anastomosed can also be due to inadvertent ligation of terminal vessels supplying the edges, incorrect angle of division, or too generous trimming of the mesenteric border [7].

In this chapter we will review the most commonly encountered vascular patterns and their variations, highlighting how these variants may influence the vascular supply to the remaining colorectal structure during the most commonly performed colorectal resections and the consequences for the surgeon performing colorectal surgery.

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18.2 Normal (Traditional) Anatomy

The most prevalent vascularization (approximately one-third of the population) of the terminal ileum, colon, and rectum (main organs involved in colorectal surgery) relies on vascular supply from the superior and inferior mesenteric arteries (SMA and IMA, respectively). The SMA runs off the aorta opposite L1 and supplies blood to the terminal ileum, the cecum, the ascending colon, and the proximal half to two-thirds of the transverse colon by the main branches of the SMA (the middle colic, the inconsistent right colic (less than 50%), the ileocolic arteries and the terminal branches of the SMA) [8]. The IMA runs off the aorta at the level of L3 and supplies blood to left half to left third of the transverse colon, the descending, the sigmoid colon and the upper third of the rectum by its main branches, namely the left colic, the sigmoid and the terminal, upper rectal artery.

18.2.1 Branches of the SMA

The MCA, usually the second branch of the SMA (after the inferior pancreaticoduodenal artery), normally gives rise to two branches, a right (relative to the patient) branch that anastomoses with the right colic (when present) or the ascending branch of the ileocolic terminal division, and a left (relative to the patient) branch that anastomoses with the ascending or right divisional branch of the left colic artery, forming Drummond's arcade or anastomosis, also called the peripheral arterial arcade [9] (Fig. 18.1).

The watershed of marginal blood flow between the SMA and IMA lies somewhere near the splenic flexure and has been called the Griffiths' point [6, 9] (circle in Fig. 18.1). Of note, this watershed anastomosis can be absent or insufficient in up to 40% of patients. The marginal artery of Drummond is absent in 5% of patients or can sometimes either be replaced or complemented by other arcades such as the so-called Riolan or the meandering artery of Moskowitz, often when Griffiths' point is absent or insufficient. These complementary connections are called the proximal mesenteric arcades. Likewise, there is another critical secondary watershed area between the vascular supply coming from the most distal sigmoid artery and the most proximal branch of the superior rectal artery called Sudeck's critical point [9] (dotted circle in Fig. 18.1). This anastomosis is insufficient or absent in up to 15% of patients.

The right colic artery, when present, gives rise to two pericolic marginal branches, one ascending, connecting with the right branch of the

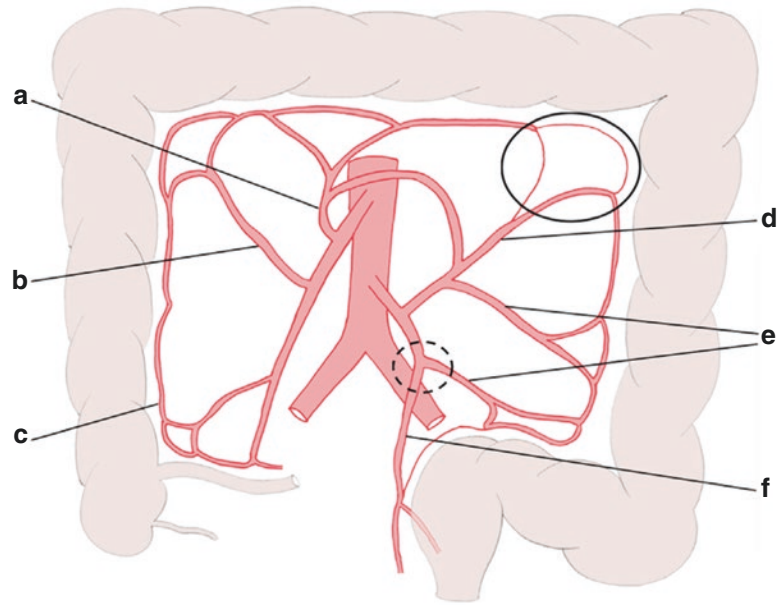

Fig. 18.1 Normal colonic vascularization [9]. Griffiths' (full circle) and Sudeck's (dotted circle) points are critical watershed vascular connections that warrant attention during colonic resection: (*a*) middle colic artery; (*b*) right colic artery; (*c*) ascending branch of the ileocolic artery; (*d*) left colic artery; (*e*) sigmoid arteries; (*f*) superior rectal artery; full circle: Griffiths' point (no vascular connection in up to 53% of patients); dotted circle: Sudeck's critical point (no vascular connection in up to 15% of cases)

MCA, the other descending, connecting to the ascending branch of the ileocolic artery.

The ileocolic artery divides into an ascending branch that irrigates the cecum and appendix, and anastomoses with the right branch of the middle colic or right colic artery and a descending branch that goes to the terminal ileum.

18.2.2 Venous Circulation

Right colon: Normally all arteries have their nominal venous counterparts (middle colic vein, right colic vein (more consistent than its arterial equivalent), ileocolic vein). While the ileocolic veins usually drain directly into the superior mesenteric vein, the middle colic and right colic veins drain into a common trunk called the Henle trunk that usually runs directly into the superior mesenteric vein [8] (Fig. 18.2).

Left colon: Normally all nominal venous counterparts (left colic vein, sigmoid veins, and superior rectal vein) drain directly into the inferior mesenteric vein (Fig. 18.2).

18.2.3 Most Frequent Variants

Variations can be due to different congenital or acquired anatomic configurations (after colectomy, gastrectomy, pancreatic resection, or sometimes even radical nephrectomy) or changes induced by chemo/radiation therapy or disease (atherosclerosis).

The MCA can be completely absent (25%) [7, 11], the two branches can arise directly from the SMA (without a common trunk), one or the other can be absent, or there is no communication between the two branches (5–10%) (Fig. 18.3). The right colic artery is absent in up to 1/3 of cases. The communication between the SMA and IMA at the splenic flexure (Griffiths' point connection) can be absent or inadequate in 43 to 53% of cases [6, 12–14].

The ileocolic artery can pass in front of (≈30%), or behind (≈60%) the superior mesenteric vessels (Fig. 18.3) [15]. This has its importance when lymph node dissection of the origin of the ileocolic vessels is envisioned, notably in complete mesocolic excision.

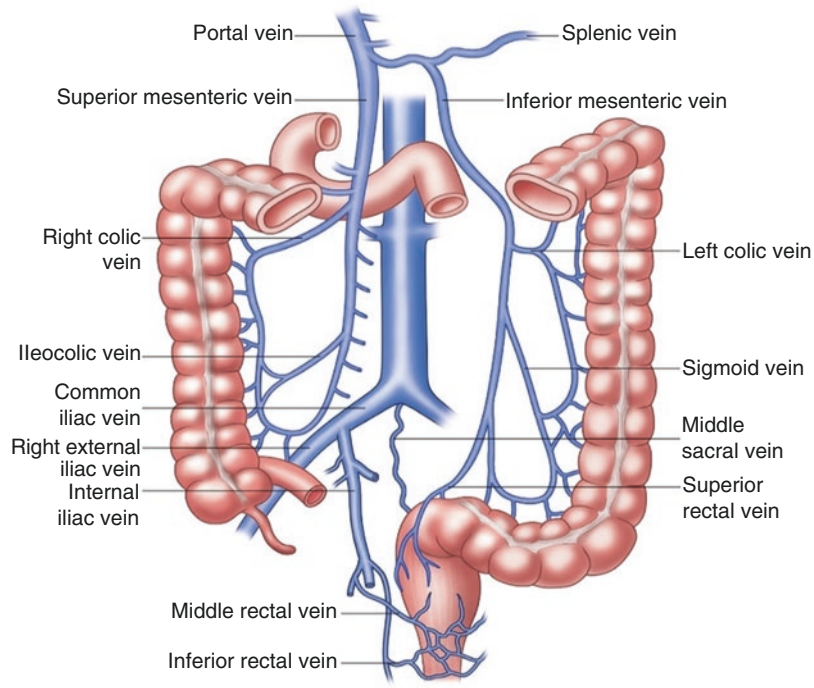

Fig. 18.2 Right and left colonic venous networks [10]

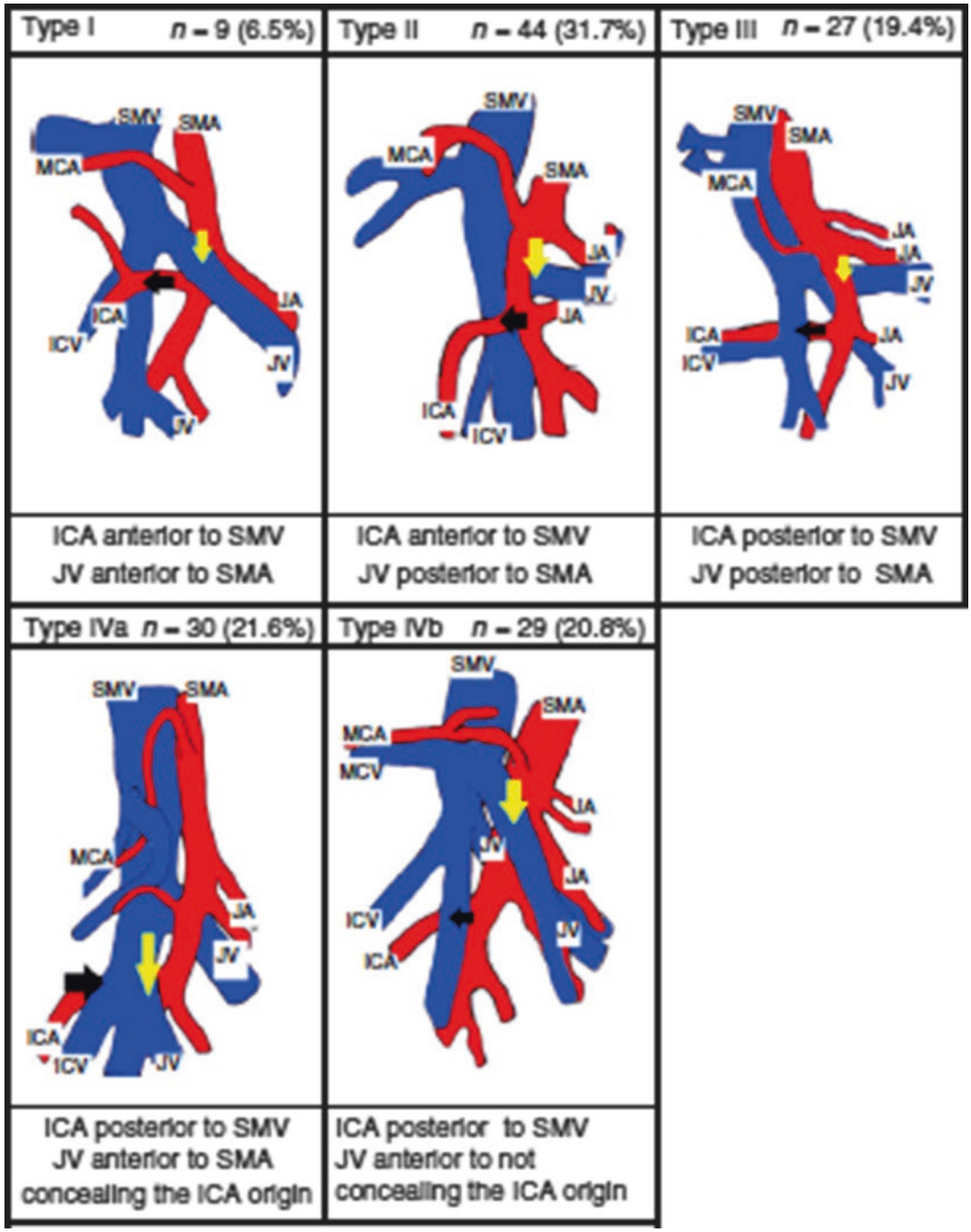

Fig. 18.3 Variations in the position of the ileocolic vessels [15]

The vascular problems of concern can arise from the level of ligation of the inferior mesenteric artery (preservation or not of the left colic artery), preservation or not of the superior rectal artery, integrity of the arcade of Drummond, Griffiths' point, Sudeck's point, variations in the anatomy of the MCA, and problems created when patients have atherosclerosis, or have had

chemotherapy/radiation therapy (in particular within the previous 6 months), embolization (colonic bleeding) or prior surgery (gastrectomy, pancreatectomy, radial nephrectomy and in particular, previous colectomy), when the origins of the main feeding vessels have been ligated (previous surgery), or are insufficient (atherosclerosis, median arcuate syndrome, previous radiation, or when related to the direction of flow through the vascular network.

Usually the colonic vascularization is not affected by the median arcuate ligament syndrome [16]. However, when the hepatic vascularization is dependent on a right hepatic artery arising from the superior mesenteric artery, or when the celiac axis vascularization is dependent on retrograde flow through the pancreaticoduodenal arcades, attention is warranted to correctly identify the middle colic (and eventually the right colic) vessels, remembering that the first branch off the SMA may be the inferior pancreaticoduodenal arcade, and that the origins of such aberrant hepatic vascular supply may complicate the identification of the MC vessels.

Both the origins of the SMA and IMA can be stenotic, usually due to atherosclerosis (intrinsic stenosis). In case of stenosis of the origin of the IMA, antegrade flow from the SMA through the marginal arcade or when Griffiths' point is insufficient or absent through the proximal mesenteric arcade, retrograde flow from the internal iliac arterial flow originating from the middle and inferior rectal arteries through the superior rectal artery can be present and warrants attention when division of the marginal arcade or the superior rectal artery is envisioned.

In case of SMA stenosis, vascular supply is taken up by the celiac axis via the pancreaticoduodenal arcades and jejunal arteries. Retrograde flow also exists from the IMA through the proximal and peripheral marginal arcades.

When both the SMA and IMA are stenotic, the colonic vascular supply is essentially based on backflow from the celiac axis through the pancreaticoduodenal arcades and jejunal arteries, and/or, to a lesser degree, from the internal iliac arteries via Sudeck's point.

The typically four-branched gastrocolic trunk of Henle (right gastro-omental vein, right colic vein, middle colic vein, and pancreaticoduodenal vein) exists in about 8 out of 10 patients. Wide variations exist, a gastrocolic trunk in one-third, a gastro-pancreatic trunk in 10%, and a gastro-pancreatico-colic trunk in a little more than 50%.

18.3 Impact on Colectomy

Under normal conditions (patient non atherosclerotic, no previous chemo/radiation therapy, no prior colectomy), both left and right colectomies are straightforward.

Transverse colectomy is a bit more tricky, as the limits of resection depend on whether the tumor is located in the left or right half of the transverse colon and the patency of the marginal artery after division of one, both or the common trunk of the MCA, or the Griffiths' point for vascularization coming from the left colic artery. The proximal segment is vascularized by the anastomoses arising from the ascending branch of the ileocolic artery for right-sided resections, and on the MCA and the marginal artery for left-sided resections.

18.3.1 Left Colectomy

The vascular supply to the proximal and distal segments to be anastomosed after left colectomy depends on whether the colectomy is segmental or a hemicolectomy. There is an ever-ongoing debate as to whether it is better to perform a high-tie (between the aorta and the left colic artery run-off) or low-tie (below the left colic artery run-off) ligation of the inferior mesenteric artery. Protagonists for one or the other base their arguments on the theoretical radicality of high-tie with regard to carcinologic principles or the extra length procured for the proximal segment versus those who argue that there is no statistically significant difference in survival between the two, or that extra length comes essentially from the ligation of the inferior mesenteric vein, more than the arc of the left colic artery when left intact.

18.3.2 Right Colectomy

For simple ileocecal resections, vascular variations or disease do not have notable consequences on the vascular supply to the remaining terminal ileum or the distal transverse colon.

The absence of the right colic artery has little if any consequences on the outcome of right-sided colectomies.

Problems arise however, when the MCA is absent, and the vascular supply to the right portion of the transverse colon and the hepatic flexure is dependent on the marginal artery (blood coming from the IMA via the left colic artery), or the secondary arcades (Riolan or Moskowitz) that must be preserved when the peripheral connection is absent or deficient. This means that lymph node dissection proximal to these arcades has to be extravascular.

18.3.3 Colonic Resections in Patients with Vascular Disease

18.3.3.1 Left Colectomy in the Vascular Patient

The splenic flexure vascular network can be a problem as the risk of ischemia of the mobilized colon is about 40% because of insufficient upstream vascular supply from the middle colic vessels through the Drummond arcade and the right branch of the left colic artery (Griffiths' point). In these patients, one should consider preservation of the left colic artery (this artery may be the only source of splenic flexure vascularization). Likewise, when present, a more proximal mesenteric arcade (Riolan or Moskowitz) should be preserved (may be the only source of blood supply to the transverse and right or left colon).

Onset of ischemia of the left portion of the transverse colon during segmental colectomy dictates the need to extend the colectomy to a true left hemicolectomy. In these cases, the proximal colonic segment may be too short for a traditional pre-mesenteric anastomosis and may then require a trans-mesenteric anastomosis (Toupet technique) [17], sometimes called retro-mesenteric anastomosis by Romberg or mobilization and inversion of the entire right colon (Deloyers technique) [18, 19]. Of note, the trans-mesenteric procedure requires full mobilization of the proximal transverse colon and that the MC vessels are intact [20]. Patients with poor hemodynamics during the procedure should not have an anastomosis and undergo a Hartmann procedure.

Patients with aortic bifurcation thrombosis (Leriche syndrome) are at risk of lower limb ischemia when there is no vascular intercommunication between the last sigmoid artery and the superior rectal artery (Sudeck's critical point) [9]. These patients require a revascularization of their lower limbs prior to colonic surgery, or if this is not possible or done, the vascular division of the colonic mesentery should be performed as close as possible to the intestinal wall.

18.3.3.2 Right Colectomy in the Patient with Vascular Disease

For patients requiring a right colectomy including the hepatic flexure, the MCA must be preserved to avoid devascularization of the left transverse colon. If this is not possible and ischemia onsets, total colectomy may be the only solution.

18.3.4 Consequences of Previous Surgery

18.3.4.1 Left Colectomy in a Patient with Previous Right Colectomy

In patients scheduled for left colectomy but who have already undergone a right colectomy, it is important to know whether or not the middle colic and/or the right colic arteries were preserved or not. Preoperative vascular mapping may be necessary. If one or both of these arteries were not preserved, and/or the patient requires a more extensive colectomy, it is imperative that the left colic artery be preserved. If this is not possible, then a total colectomy is needed [9].

18.3.4.2 Right Colectomy in a Patient with Previous Left Colectomy

Ileocecal resection for cecal carcinoma with preservation of the hepatic flexure can usually be performed safely as long as the middle colic vessels or a left colonic artery and marginal arcade are intact. This determines whether the remaining transverse colon can be preserved or not. If the middle colic and/or the right colic artery are not intact, total colectomy with ileorectal anastomosis is required [9].

18.3.5 Strategy for Oncologic Lymph Node Dissection in Patients with Colonic Cancer

In patients who have had a previous colectomy (right or left) and/or who have a history of vascular disease and must undergo colectomy for colon cancer, the indications for lymph node dissection must be carefully pondered case by case.

1. In a patient with previous colectomy but no vascular disease, or with vascular disease but without aortic bifurcation thrombosis (or when surgical or endovascular extremity revascularization is possible), oncological rules should be observed including oncologically sound lymph node dissection.
2. In a patient with aortic bifurcation thrombosis when lower extremity revascularization is not possible, total colectomy must be envisioned.

18.4 Technical Aspects

As for any intestinal resection, tissue vascularization must be evaluated as the operation progresses. Whatever type of resection is proposed, temporary vascular clamping at the proposed ligation area should be performed prior to any definitive mesenteric division, confirming the persistence of a pulse distally, as detected by direct palpation or Doppler probe. Similarly, after arterial transection, intraoperative assessment of the junction between well- and poorly vascularized bowel will help to identify the optimal level at which the colon should be divided. This is where techniques currently under evaluation to assess the vascularization of the colon (indocyanine green) or to assess lymph node involvement and thereby limit the extent of node dissection (indocyanine green, sentinel lymph node technique) could be of major interest [21].

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19 Prophylactic Resections for Genetic Predisposition of Colon and Rectum

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19.1 Introduction

Prophylactic surgery aims to eliminate the target organ before the life-threatening disease develops, to increase the expected survival and prevent the decrease in the quality of life. Various etiologies can be candidates for prophylactic surgery. The purpose of prophylactic surgery in diseases of the colon and rectum with a genetic predisposition for malignancy is the excision of the organ at risk before malignancy develops. In case of detection of malignancy in the organ to be resected, the name of the surgery will be definitive surgery, not prophylactic. In prophylactic surgeries to be performed due to the risk of developing malignancy, oncological principles must be applied, as in definitive operations.

Hereditary and familial colorectal polyposis syndromes in the colon and rectum offer indications for prophylactic surgical interventions. The hereditary colorectal syndromes discovered about 100 years ago when Alfred S. Warthin described Hereditary Non-polyposis Colorectal Cancer Syndrome (HNPCC), which is now known as Lynch Syndrome (LS) [1]. The molecular structure of the diseases was first understood by the report of the Familial Adenomatous Polyposis Syndrome (FAP) by exposing the APC gene located on the 5q chromosome Groden after 1990s [2]. Subsequently, respectively Lynch syndrome was identified by determining the MLH1/MSH2/MSH6 mutations in 1993, Peutz–Jeghers syndrome (PJS) was identified by determining the STK11 in 1998, and Juvenile Polyposis (JP) syndrome was identified by determining SMAD4/BMPR1A mutations in 2001 [3–6]. Although there are some changes in nomenclature over time due to different phenotypic, genotypic, histopathological and clinical presentations, it has been preferred to categorize the syndromes based on the polyp structure in the current literature. Today, it will be more accurate to evaluate the situations which are candidates for prophylactic surgery, with the newly defined different subgroups (hereditary adenomatous polyposis syndromes, MUTYH associated polyposis, polymerase-proofreading associated polyposis, Lynch syndrome, familial colorectal cancer type X, etc.) which surgical options may be performed, together.

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19.2 Hereditary Adenomatous Polyposis Syndromes

19.2.1 Familial Adenomatous Polyposis Syndrome

It is characterized by more than 100 adenomatous polyps that become adenocarcinoma, the incidence is 1/7000–12,000 in newborn, and the ratio of female/male is 1 [7]. Polyps mostly appear in the second or third decade. The average age of diagnosis is 36, and the average age for the appearing first polyp is 16 [8, 9]. Clinical presentation may be in three types: early childhood, 15–25 years old, and late (mild) onset [10]. At the time of diagnosis, 90% of polyps are smaller than 0.5 cm, and less than 1% are larger than 1 cm. Adenomas transform into cancer 100%. Epidermoid cysts, osteoma in bone, desmoid tumor, gastric fundic polyp, and congenital hypertrophy of retinal pigment epithelium may be seen as extra-colonic involvements of FAP [11]. The variant accompanied by a brain tumor and medulloblastoma is known as *Turcot Syndrome.* The histopathological feature is that they are dysplastic or adenomatous epithelial cells seen in portions of single crypts that are not found in polyps in the healthy population and are called as *microadenomas* [7].

Genetic tests are carried out for making a diagnosis in two situations:

1. For testing individuals with polyposis for whom a clinical diagnosis is uncertain; individuals with more than 10 adenomas or sometimes with extra-colonic manifestations but no underlying pathogenic mutation.
2. To the family of the individual with the known germline mutation; while positive result provides the diagnosis of the syndrome, in a negative result, the syndrome is excluded.

In the case of suspected adenomatosis, APC and MUTYH gene mutation analysis should be performed [12]. In FAP, an allele is mutated; adenoma formation occurs if the secondary allele is damaged or deleted due to a somatic event. Increased adenoma-carcinoma sequence after APC reactivation is similar to K-ras, p53, and chromosome 18 mutation in FAP and sporadic cancer. Although mutations are scattered throughout the APC gene, most mutations appear at the 5′ end of exon 15 called the cluster region [13, 14].

Surveillance in affected families should be initiated from puberty [15, 16]. Prophylactic surgery should be considered in the circumstances such as severe polyposis burden, severe dysplasia, tubule-villous histopathology, multiple adenomas greater than 5 mm and bleeding, diarrhea, retarded growth, anemia, and severe stress [17]. Colectomy with or without proctectomy is recommended for the treatment. If the count of rectal adenoma is less than 20, the count of colonic adenoma is less than 1000, and there are genetic mutations between 1252 and 1464, proctectomy may not be required [17]. Nevertheless, prophylactic surgery can be postponed in patients who are well selected, whose adenomas are less than 5 mm, who have a family history of aggressive abdominal desmoid tumors, and who are entirely asymptomatic, because complications related to desmoid tumors can be more mortal than colorectal cancer development [18]. However, FAP patients are generally operated in their 20s, and as a result of this strategy, desmoid tumors and upper gastrointestinal system (GIS) cancers are among the causes of mortality and morbidity in these patients [19].

Desmoids are non-metastatic locally invasive myofibroblastic proliferations, and although they can be settled in any localization, they occur especially in the small intestine mesentery and abdominal wall in patients with FAP. Intra-abdominal desmoids can lead to urological or intestinal obstruction and sometimes undergo necrosis [20]. In FAP patients, 80% of desmoids occur until 35 years of age, on average 3.2 years after prophylactic surgery of the large intestine (min 6 months, max. 9 years) [21]. According to this study, routine imaging is not performed for desmoids.

Upper GIS polyps are most common in the periampullary region, and follow-up of patients should begin with endoscopy and biopsy of suspected polyps at the age of 25–30. Although

options are endoscopic mucosal resection, snare ampullectomy or trans-duodenal excisions, endoscopic ablation generally requires a large number of sessions, and recurrence is high after all of three [22]. For papillary or duodenal adenomas with persistent or recurrent high-grade dysplasia, pancreas-preserving duodenectomy or pancreaticoduodenectomy is recommended [17]. In progressive tumors, and unresectable diseases, cytotoxic chemotherapy can be applied, and surgery can be combined [23].

Long-term use of chemopreventive agents instead of surgery is not recommended in the primary treatment of FAP. Even so, non-steroidal anti-inflammatory drugs such as sulindac, celecoxib, rofecoxib, and exisulind have been shown to reduce the number and size of polyps [24]. The number of colorectal polyps decreased by 28% in patients with FAP, which are treated with selective cyclooxygenase-2 inhibitor celecoxib twice a day for 6 months [25]. In a randomized, placebo-controlled, double-blind study, genotype (+) patients were examined, and it was reported that sulindac did not affect subsequent colorectal polyposis development. Also, in patients with rectal polyps that were somehow controlled by the sulindac effect, even so, rectal cancer has developed. Finally, patient compliance is required for the regular use of these drugs and can cause serious side effects [26]. However, the use of these drugs can reduce the load of polyps and facilitate endoscopic management of polyps in patients with an ileal pouch, high-risk rectum left, or refusing proctectomy.

19.2.2 Attenuated Familial Adenomatous Polyposis Syndrome (AFAP)

The count of adenomatous polyp is 10–99, and it is inherited autosomal dominant. The number of polyps is on average 25, and generally, the tendency to locate on the right colon is high. It is caused by APC mutations in localizations such as far proximal 5′ end of the gene, the far distal 3′ end of the gene, or in certain locations of exon 9 [27]. Complete or partial deletions lead to AFAP. The age for adenomas to appear is 10–20 years later than FAP. The cumulative lifetime risk of developing CRC is 69%. The average age of occurrence is 55–58 [27]. In the treatment, there may be no need for any surgical intervention by performing repeated colonoscopic polypectomies. Prophylactic surgery is required either in the case of the presence of multiple adenomas that cannot be controlled endoscopically or if the adenomas are more extensive than 6 mm and in the case of severe dysplasia or suspected cancer.

19.2.3 MUTYH Associated Polyposis (MAP)

MAP has an autosomal recessive inheritance. It is caused by biallelic pathogenic germline variants in the base excision repair MUTYH gene [28]. The most common forms are Y179C and G396D [29–31]. Patients usually develop between 20 and 99 polyps. The clinic is most often revealed by the fifth or sixth decade [32]. Cancer develops in 40% of MAP patients, and lifetime cumulative colorectal cancer (CRC) incidence is 70–75% [33]. Less than 1% of CRC patients are homozygous for MAP. In those who are heterozygous, the risk of CRC increases to 5–7%. MUTYH variants have also been identified in patients who developed CRC without detecting colorectal polyp [34]. Upper GIS tract polyps may accompany the clinic. For the diagnosis, a test is performed for MUTYH pathogenic germline mutation. Surveillance takes place with colonoscopy every 5 years from the age of 40 or 10 years before the first diagnosis of the individual with MAP in the family [35]. Endoscopic polypectomies are performed in the treatment, and prophylactic surgery is recommended in cases where endoscopy is not sufficient.

19.2.4 Polymerase-Proofreading Associated Polyposis

It is a newly defined syndrome that causes CRC and endometrial cancer at a young age. In a recent study involving 858 early-onset patients, a

new POLD1 mutation and a known POLE mutation were identified. It appears to be dominantly hereditary and with high penetration power [8, 36]. There is no consensus regarding its treatment and surveillance. The frequency of polyps, cancer, and extra-colonic phenotype have not been revealed yet. However, it seems that close endoscopic surveillance and prophylactic surgery will be required.

19.3 Hereditary Non-Polyposis Colorectal Cancer

It is the most common form of hereditary colorectal cancer and the cause of 3% of colorectal cancers and also referred as Lynch syndrome. It is an autosomal dominant inheritance predisposing syndrome for cancer with no clear clinical findings except for solitary adenomas that may develop cancer. It has been called as *Hereditary Non-polyposis Colorectal Syndrome* since the 1980s because Lynch used this name to distinguish the disease from other polyposis syndromes. However, with the understanding that the disease is characterized by colorectal polyps, only the definition of Lynch Syndrome has recently been established in the literature. DNA repair genes (MMR) such as MLH1, MSH1, MSH6, and PMS1 are mutated [37]. While the lifetime cumulative CRC risk in MMR (+) individual is 4% for 5 years, 10% for 10 years, the risk is 0.04% and 2% for those with MMR (−), respectively [38]. The average age at which cancer appears is 46, and the risk of developing extra-colonic cancers is around 5–15% [39]. Patients with a young age presentation can be explained by the fact that the adenoma-carcinoma sequence, which is 7–10 years in sporadic cancer, is 35 months in LS [40]. Synchronous and metachronous secondary tumors exist in more than 35% of the patients [41]. Affected individuals may have 43% endometrium, 19% stomach, 8% urinary tract, and 9% ovarian cancer [42]. Also, patients should be evaluated for tumors of the kidney, small intestine, biliary tract, and brain [43]. The phenotype of osteomas, congenital hypertrophy of the retinal pigment epithelium, dental cysts, and sebaceous gland tumors has been named *Muir–Torre Syndrome* [44].

Clinical and pathological features alone are not sufficient in diagnosis; family history is important. *The Amsterdam criteria* were defined for the diagnosis in 1991, and the second was revised and published in 1999, accordingly:

- Diagnosis of colorectal cancer in at least three relatives, at least one of which is the first degree.
- Presence of affected family members in at least two generations.
- At least one of these cancer patients is diagnosed before age 50.
- Endometrium, small intestine, or uroepithelial cancer accompanying colorectal cancer to exclude FAP diagnosis [45].

It is important to know that only 60% of families meeting the Amsterdam criteria have an inherited anomaly in an MMR gene [46]. Demonstration of microsatellite instability (MSI) supports MMR gene mutation, and immunohistochemical (IHC) assessment shows which gene the mutation is in [47].

The Bethesda criteria defined in 2004 were developed to identify the MSI-high status by MSI or IHC, in individuals who undergo genetic testing for the diagnosis of LS [4, 8, 48]. Provides a scanning approach with 70% precision, accordingly:

- Having a diagnosis of CRC before the age of 50.
- Presence of LS-associated synchronous or metachronous tumor.
- Having a CRC with MSI-high histology before 60 years of age.
- LS-related tumor or CRC diagnosis in one or more relatives of the first degree before the age of 50.
- LS-associated tumor or CRC in two or more relatives of first or second degree, at any age.

Surveillance is performed every 1–2 years with colonoscopy starting at the age of 20–25. After the age of 40, the evaluation should be done

every year with endometrial vacuum biopsies combined with endo-vaginal USG [49]. Prophylactic surgery is recommended in treatment due to increased risk of CRC, metachronous cancer, and increased adenoma-carcinoma sequence speed [41]. For this reason, subtotal or total abdominal colectomy has been advocated over segmental colectomy to offer the advantage of decreased risks of metachronous lesions [50]. Risk-reducing surgery is defined as the approach in which organs with a high risk of developing cancer are resected. Although surgery for the risk of the endometrium and ovarian cancer is not recommended for Lynch syndrome in the European perspective, prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy are recommended for women who are postmenopausal or who do not intend to have children, in the USA.

19.3.1 Familial Colorectal Cancer Type X

It is used to identify patients who meet the Amsterdam criteria but whose MMR defect cannot be detected [51]. These family members appear to have a lower incidence of colorectal cancer relative to individuals belonging to a family in whom an MMR mutation has been detected. It is presented with, the advanced age of occurrence, rarely metachronous CRC, and a lower risk of extra-colorectal tumors [51–53]. Prophylactic surgery is not recommended except for preneoplastic changes unless there are a germline mutation and phenotypic identification in individuals at risk.

19.4 Hereditary Hamartomatous Polyposis Syndromes

Hamartamatous polyposis syndromes are Cowden syndrome, Bannayan–Ruvalcaba–Riley syndrome, Peutz–jeghers syndrome, and Juvenile polyposis syndrome, which are not very common and differential diagnoses can be made between them by minor clinical differences.

19.4.1 Peutz–Jeghers Syndrome

It is characterized by hamartomatous intestinal polyposis and typical mucocutaneous hyperpigmentation. It is autosomal dominant disorder. Its incidence is 1/80,000–200,000 in newborns, lifetime cumulative CRC risk is 39%, and the average age of emergence is 44 [54, 55]. An erroneous diagnosis of cancer due to epithelial folding can be made and defined as *pseudo-invasion* [56]. The localization of polyps is small intestinal 94–98%, colon 25–30%, stomach 21–25%, and rectum 22–25%, respectively [57]. GIS polyps exist in 88–100% of patients, and the risk of malignancy has increased 100–400 times compared to the healthy population [58]. In affected family members, surveillance is performed biennially with upper and lower GIS endoscopies. Colonoscopies are initiated at the age of 8–12 years.

19.4.2 Juvenile Polyposis Syndrome

It is characterized by a large number of polyps in the colorectal region, stomach, and small intestine [59]. Its incidence in newborns is 1/10,000. It is autosomal dominant inheritance. The risk of CRC has increased 34 times in JP, and the cumulative lifetime risk is 30–50% [60]. The average age of diagnosis is 42. Although at some patients, it may be seen less frequently, an average of 50–200 polyps are seen, and they may be in different sizes from 1–2 mm to 3 cm. Polyps are found 98% in the colorectum, 14% in the stomach, 7% in the jejunum and ileum, and 7% in the duodenum [61]. The risks of developing malignancy are 9–50%. Diagnostic criteria:

- presence of at least 5 polyps located in the colorectum.
- juvenile polyps in other regions of GIS.
- detection of any number of juvenile polyps in an individual whose family history is known.

Genetic testing enables diagnosis, evaluation of family members, as well as differential diagnosis with Cowden syndrome and Bannayan–

Riley–Ruvalcaba syndromes [12, 62]. While 75% of new diagnoses have a family history, 25% have novo mutations and are sporadic [57]. In treatment, excision of all detected polyps should be done. In cases that cannot be controlled endoscopically, prophylactic surgery should be considered. The aim is not only to reduce the risk of cancer but also to prevent complications such as anemia, diarrhea, and intussusception.

19.4.3 Cowden Syndrome

It is characterized by multiple GIS hamartomas and ganglioneuromatosis. The presence of polyps ranging from several polyps to several hundred can be seen. While the most common type of polyp is hamartomatous with 29%, juvenile, ganglioneuroma, adenoma, inflammatory polyp, leiomyoma, lipoma, lymphoid polyp, and rarely hyperplastic polyps are also detected [63]. There are different variants such as Bannayan–Riley–Ruvalcaba syndrome and PTEN hamartomatous tumor syndrome (PHTS). Widespread glycogenic acanthosis in the esophagus can be seen in PHTS at 80%. In genetic tests, PTEN mutation is examined. PTEN (+) individuals should also be screened for colon, upper GIS, thyroid, breast, uterus, kidney, and skin cancers. It has been reported that the risk of CRC is increased by 13% in PTEN (+) individuals before the age of 50 [63]. The average age of emergence is 44–48.

19.5 Serrated Polyposis Syndrome

Its incidence in newborns is 1/100,000. Its frequency was found to be 0.66% in a large population-based series. Also, this rate was found to be 0.34% in a Spanish study [64]. The lifetime cumulative CRC risk is 50% [65]. The average age of diagnosis is 48 years. There is a 70% tendency to hold the right colon. Clinical diagnosis can be made by:

- more than 5 polyps, at least two of which are greater than 10 mm in the proximal of the sigmoid colon,
- serrated polyp history in first-degree relatives,
- the presence of more than 20 serrated polyps in different localizations in the colon.

NCCN guideline recommends starting surveillance in first-degree relatives:

- at the age of 40,
- the earliest diagnosed SPS in the family,
- 10 years before the age of the person diagnosed with SPS-related CRC.

According to ACG 2019 guidelines, the conditional recommendation is recommended with a low level of evidence for SPS patients under surveillance, performing colonoscopy every 1–3 years and removing adenomas larger than 1 cm [12]. Patients who cannot be controlled endoscopically and have high-grade dysplasia should be evaluated for prophylactic surgery [66].

19.6 Hereditary Mixed Polyposis Syndrome (HMPS)

It presents with a different clinical picture in which hyperplastic, serrated polyps, and adenocarcinoma exist together. It occurs in Ashkenazi Jews. The average age of emergence is 28. Differential diagnosis should be made with JPS and SPS. Although HMPS is thought to occur due to the localized CRAC1 gene mutation in the 15th chromosome, recently, two patients were found to have colorectal polyp predisposition due to localized GREM1 gene duplication in the 15th chromosome. Prophylactic surgery is planned for patients who cannot be managed endoscopically in the treatment [12].

19.7 Genetic Evaluation

Predictive genetic testing of family members at risk is possible after reliable identification of the relevant mutation in the family. Thus, while appropriate surveillance or prophylactic treatment can be recommended for mutation-positive

individuals, monitoring of mutation-negative individuals can be terminated. Another benefit of genetic screening is that long-term cost-effectiveness and accuracy rate are higher than endoscopic screening. Also, genotype-phenotype differences of syndromes can help in planning the surgical option according to the determined mutations. In the Dutch study, it has been reported that patients with 3′ codon mutations in FAP patients have a 1250-fold higher risk of rectal cancer than those with mutations in the 5′ codon. These patients have been reported to have a high risk of secondary rectal cancer and rectal polyposis after total colectomy [16, 65].

The localizations in which errors are most prominent in tumor DNA are microsatellites. MSI detection is the gold standard for detecting impairment of tumor DNA [47]. MSI testing is a polymerase chain reaction (PCR) based test that tests for allele shift in a standardized panel of markers. If the allelic shift ratio is 30% or more, MSI is defined as high; if the ratio is 0%, MSI is defined as stable; and if the value is between 0%–30%, MSI is defined as low. IHC tests can be performed on tumor tissue to detect the presence or absence MMR proteins. In LYNCH syndrome, if patients who have CRC accompanied by MMR mutations in the subsequent IHC assessment, it is recommended to be imaged by MSI analysis of tumors. An abnormal IHC test has a 100% predictive value for MSI elevation [67–69].

Testing for hereditary colorectal syndrome in the family may cause anxiety among relatives [70]. Despite careful personal counseling, mutation (+) individuals tend to misunderstand the emergence of cancer possibility. Therefore, obtaining consent for individual counseling and testing is essential for possible undesirable effects of the test. It is essential to obtain consent from parents, especially in JP, PJS, and FAP syndromes, where the test should be done before early adulthood.

According to recent studies, different effects of BRCA 1 and BRCA 2 mutations on CRC's genetic predisposition have been reported. Even if there are studies showing that BRCA 1 and BRCA 2 are associated with increased risk of mucinous CRC, the risk of CRC was reported as not increased in both mutation carriers, according to a meta-analysis. In another meta-analysis, an increased risk of CRC was reported in the BRCA 1 mutation [71–73].

19.8 Surgical Procedures

Phenotypic expression, penetration depths, and differences in the development of the disease indicate that the content and timing of the prophylactic colorectal surgical procedure should be significantly different. The reduction of the overall risk, the possibility of compensating for organ loss, and the effects of surgical intervention shape the choice of prophylactic procedures.

Surgical options are:

- Segmental colectomy.
- Proctectomy.
- Subtotal colectomy.
- Total colectomy-ileorectal anastomosis (TC-IRA).
- Total proctocolectomy (TPC)—permanent ileostomy.
- Restorative proctocolectomy-ileal pouch-anal anastomosis (RPC-IPAA).

Appropriate procedure selection is made by considering postoperative functional results, preoperative anal sphincter status, and patient's preference. All of the techniques reduce the risk of malignancy, improve the quality of life and can be applied with minimal invasive or open techniques. Nowadays, it is recommended to use minimally invasive surgical techniques, if possible, and access to the bladder and pelvic organs can be achieved with extensive adhesiolysis by experienced hands, even if there is previous abdominal surgery history. Minimally invasive techniques have advantages of decrease in inflammatory mediators, improved pulmonary functions, faster return of bowel function, and reduced hospital length of stay when compared to the open techniques.

TC-IRA: It may be preferred in patients with low rectal load, who has less than 1000 colorectal polyp, and less than 20 rectal adenomas [49, 74, 75].

Indications for adding proctectomy to colectomy are:

1. more than 1000 polyps in the colon,
2. presence of more than 20 adenomas in the rectum,
3. the size of adenomas more than 3 cm,
4. severe adenomatous dysplasia,
5. villous adenoma development [76].

TPC/End ileostomy: It is rarely the first option. Preferred conditions are cancer that invades the pelvic floor or sphincter, an unacceptably weak anal sphincter function, lack of performing ileal pouch technically due to desmoid involvement or excessive shortness of the mesentery. Sometimes it can be consciously preferred by patients who need to undergo proctectomy, on the grounds that their intestinal habits will increase 5–6 times a day permanently.

It should be taken into consideration that the risk of rectal cancer increases 4–8% in 10 years and 26–32% in 25 years, especially after FAP, by leaving the rectum in situ after TC-IRA [76, 77]. Also, it is estimated that this information appears to be higher than usual as a result of the operations performed in the case of intensive rectal disease when TP-IPAA has not become widespread yet [78]. In recent studies, the degrees of probability for developing carcinoma are 0% in Cleveland clinic, while it is 32% in the series of the Mayo clinic and varies [79]. Besides, in the series published by Heiskanen and Jarvinen, this rate is 9%, and although the figures are different, the risk of developing cancer increases over time [15]. Endoscopic monitoring of the rectal segment at 6-month–1-year intervals is recommended in the postoperative period. Adenomas smaller than 5 mm can be observed or removed with forceps. Adenomas larger than 5 mm should be excised with a snare. However, after repeated fulguration and polypectomies, there may be a decrease in rectal compliance and difficulty in identifying flat cancers that will remain under scar tissue [49]. It is necessary to perform terminal ileostomy or IPAA following complementary proctectomy in a group of 20–50% patients with progressive polyposis, intraepithelial neoplasia, or an increased risk of early cancer [80].

Different forms of TPK-IPAA procedure, such as minimally invasive, hand-assisted, laparoscopic-assisted, single incision and ileal pouch construction, may be performed. Suitable indications are:

- adequate anal sphincter function,
- damage protective physiological defecation function,
- acceptance of multiple procedures, if required,
- BMI <25 (a thick fatty mesentery will not fit comfortably in a narrow pelvis; in addition, it may not reach the anal canal despite additional attempts to extend the pouch mesentery).
- obtaining adequate distal margin,
- absence of an emergency clinic such as bleeding, intussusception, and obstruction [81–86].

Even if the concept of using genotype-phenotype reflections is popular in FAP when choosing between TC-IRA and RPC-IPAA, it is recommended that surgical procedure preference is made considering the clinical findings due to existing phenotypic expression differences even within the members of the same family. The functional results of the surgeries should also be evaluated while making a choice. Some studies have reported increased bowel movement, passive incontinence, incidental contamination, and morbidity is associated with post-TPC-IPAA; contrarily, in some studies, it is reported that functional results and quality of life as similar [87–89]. In a recent record-based observational cohort study in which the results of 925 operated patients were examined and the frequency of choice was evaluated in a recent data-based observational cohort study, it was observed that TC-IRA was applied as 68.2% and RPC-IPAA as 36.8% [90].

Also, desmoid tumors occurring in the postoperative period seem to be an important problem in FAP patients [8]. Postoperative desmoid tumor development is thought to decrease with the use of laparoscopy and minimized surgical trauma [91]. A cohort analysis performed at the Cleveland Clinic showed that the risk of developing desmoids after IRA was less than patients who underwent RPK, and it was stated in this study that laparoscopy caused a lower risk of developing desmoids in the IRA group [92]. More limited abdominal trauma can cause a decrease in the rate of desmoid tumor formation. In the view

of this information, it should be concluded that the choice of treatment should be individualized.

For patients who can apply with the emergency clinic, total colectomy with an end ileostomy and postponed proctectomy with pouch-anal anastomosis can be preferred while preserving anorectum. In the case of massive hemorrhage from the rectal stump, RPC is rarely required, but near-total proctocolectomy can often be performed with a short rectal stump [93, 94].

Especially polyposis patients who are operated at an early age are at low risk for anastomosis leakage after TPC-IPAA since they are generally healthy after TPC-IPAA; they are not immunosuppressed and have a normal intestine except adenomas. Although a loop ileostomy means another surgery for closure and may cause postoperative complications of its own, undiverted IPAA carries a high risk of leakage. If necessary, loop ileostomy should not be avoided [95].

In terms of optimal functional results and efficiency of the anastomosis, J pouch is generally preferred. With three- or four-legged configurations of the ileal reservoir, S or W pouches can also be created, but are rarely preferred. In a study of 94 diseases, it was shown that W pouch has no superiority over J pouch in the long term.

19.8.1 Postoperative Period

Patients who have undergone prophylactic surgery are relatively young, and most will gain their preoperative bowel function gradually. Considering the prophylactic feature of surgery in these patients, maintaining a high quality of life is critically substantial. According to a meta-analysis in which the results of 1002 patients are evaluated, compared to TK-IRA, RPK was found to be disadvantageous in terms of re-operation requirement within 30 days, long-term adverse side effects and pad use due to increased bowel movements [96].

Postoperative early and late complications include pouchitis, ileus, leak, pelvic abscess, wound infection, urinary tract infection, anastomotic stenosis, fluid-electrolyte imbalance, portal vein thrombus erectile dysfunction, retrograde ejaculation, and dyspareunia. If diversion stoma is preferred, its closure may be associated with significant complications. According to the results of a study of 1504 patients, morbidity is 11% and mortality is 0.06%. More than half of the complications are related to small bowel obstruction. Factors such as the time between primary surgery and stoma closure, closure by hand or stapler anastomosis, and presence of distal dysfunctional ileal pouch may engender morbidity after ileostomy closure.

Other uncommon complications include SMA syndrome, solitary rectal ulcer, traumatic ileal ulcer syndrome, fibroid polyp, mucosal prolapse due to external compression, puborectal spasm, sacral osteomyelitis, volvulus, and pharmaco-bezoar.

19.9 Conclusion

As our knowledge about the function of the gene that causes hereditary colorectal polyposis syndromes increases, our targeted treatment protocols will develop. Under the current circumstances, especially when it comes to colon and rectum, rapid turnover in the intestinal epithelium does not give much hope for genetic treatment. Future genetic improvements may perhaps eliminate the need for prophylactic surgery and help prevent extra-colonic manifestations.

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Prophylactic Colon and Rectum Resections for Benign Pathologies

20

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20.1 Introduction

Prophylaxis is the prevention of the disease before it transpires, as opposed to the treatment of the disease. Prophylactic surgery, on the other hand, aims to prevent more complicated circumstances that may decrease the life span and quality that may occur in the future with surgical intervention. In benign colorectal diseases, the nature and course of the disease, the application of surgical intervention, and patient-based evaluation are essential in the patient who will undergo prophylactic surgery. Although there are many benign colorectal diseases described in the literature, surgical treatment comes to the fore as therapeutic rather than prophylactic in many of them. In some benign colorectal diseases, which are common in the community, surgical treatment can be considered both therapeutic and prophylactic. Surgical treatment is inevitable in the presence of certain conditions in these diseases, but the indications and timing of prophylactic surgery are controversial and may differ in various guidelines.

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In this chapter, diseases for which prophylactic surgery could be recommended for benign colorectal diseases are discussed.

20.2 Volvulus

The definition of volvulus in western literature was first described by Rokitansky as a cause of intestinal obstruction in 1841 [1]. Volvulus, in a part of the digestive system, defines the situation where the intestine rotates in its mesentery axis, partial or complete obstruction, as well as in which the blood circulation in different degrees is disturbed. While the colon is the most affected area in the digestive system, the sigmoid colon is the most affected colonic segment in colonic volvulus by 60–75% [2–5].

Colonic volvulus (CV) is the third major cause of large bowel obstruction in the world after colorectal cancer and complicated sigmoid diverticulitis [2, 6]. CV is a rare cause in the United States that accounts for 5–10% of bowel obstruction [2, 7]. In contrast, at 13–42%, in regions such as Africa, South America, Russia, Middle East, Eastern Europe, India, and Brazil, CV emerges as the cause of intestinal obstruction [3, 6–8].

Sigmoid volvulus mostly affects older male adults, with an average of 70%. These patients are often debilitated and institutionalized and are present with chronic constipation as well as underlying psychiatric and neurological diseases.

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In addition, the incidence of the disease has been reported to be high in African Americans.

If any segment of the colon has a long and loose mesentery fixed to the retroperitoneum with a narrow base, it can rotate around its mesentery. The anatomy of the mesentery is exactly as described above in the sigmoid colon, where the volvulus is most common. The twisting of mesosigmoid is considered as physiologic fewer than 180° [6]. In rotations up to 180°, leads colon obstruction and then prompt, necrosis, and consequently, perforation may occur [2, 9].

Sigmoid volvulus (SV) is an insidious disease, and the symptoms are non-specific. High suspicion in diagnosis is essential. A gradual progression of abdominal pain, distension, and nausea are often encountered; moreover, vomiting may occur days later [6, 10]. A complete blood count and electrolytes are usually normal in patients with sigmoid volvulus in the absence of gangrene, peritonitis, or sepsis. Radiographic imaging is essential in the workup of these patients. Other radiologic modalities almost completely abandoned in favor of CT scans, with the diagnosis ability in volvulus with almost 100% sensitivity and greater than 90% specificity [10–12].

20.2.1 Treatment

The treatment approaches to volvulus vary depending on the patient's complaints and admission time interval to the hospital. Urgent surgical intervention is required whether the patient has signs of perforation or peritonitis. In such cases, although the surgical technique is determined according to the stability of the patient, peritoneal contamination is critical in this circumstance.

Currently, endoscopic decompression is recommended by American Society of Colon and Rectal Surgeons (ASCRS) as the inception of non-operative therapy in patients with sigmoid volvulus without signs of peritoneal irritation. Apart from detorsion, another advantage of this intervention is to evaluate intestinal viability [13, 14]. The success rate in endoscopic detorsion of sigmoid volvulus cases has been reported to be 52%–100% [15–19]. The major constraint of this technique is the high recurrence rates after the procedure, which affects 33.8% to 84% of patients [2, 15, 18, 20, 21]. While mortality rates of planned elective surgery performed after successful decompression are 3.3%, this rate increases to 13% in emergency surgery [7, 14]. Therefore, patients who had recurrence after detorsion may be candidates for urgent surgical intervention but should be kept in mind that elective surgery chance has been lost together with higher morbidity and mortality rates.

A study by Johansson et al. (2018) reported their recurrence rates in SV as 22% after the first episode. Although they had performed elective surgery as stated in the literature after the first episode of their patients, they pointed out that some patients might have gone under unnecessary surgical intervention [14, 17, 22–24]. Besides, in Kim et al. (2020) recently published retrospective reviews, they noted that post-detorsion sigmoid colectomy was effective in restoring bowel continuity and preventing recurrence compared to the emergency surgical approach [25]. The conclusions of the 10-year retrospective research published by Bruzzi et al. (2015) support the prophylactic surgery. In this study, following a mean interval of 5 ± 2 days after successful endoscopic detorsion, elective sigmoid colectomy was performed, while morbidity was determined as 6%, no mortality was observed [26]. According to the ASCRS guidelines, after acute phase resolution, sigmoid colectomy is recommended to prevent recurrences. Consequently, elective surgery is recommended in the literature after the first episode.

Performing elective prophylactic surgery depends on the preference of the surgeon as well as the patient's acceptance of the surgery. In the SV series of 873 patients of Atamanalp et al. (2008), 436 patients were recommended elective surgery, 94 of them (21.6%) accepted this intervention [22]. Although the data are unclear, patients are generally reluctant to undergo surgical intervention. This has been described in the studies that an acceptance rate of elective surgery is between 22 and 50% [22, 27].

Generally, the recommended time interval to prophylactic surgery is 2–3 days following the

successful detorsion, or within 60 days at the longest so that the patient can be protected from undesired outcomes that may be a result of recurrence [22, 28].

The surgical intervention options of the sigmoid volvulus are diverse. Sigmoidectomy is the chief surgical approach to prophylactic surgery meanwhile it can be performed by open or laparoscopic technique. Regardless of the technique, in the sigmoid colectomy, the crux of the matter is that the length of the sigmoid colon in which resection must be the maximum length allowing a tension-free anastomosis without requiring a left colon mobilization. The optimal length of the colon to be resected is critical, unwillingly the surgeon may face recurrences after a planned surgery. While recurrence rates were reported between 14% and 18.2% in patients undergoing non-definitive surgery, recurrences were reported as 3% despite definitive surgery in a literature review [2, 17, 29]. In a study by Larkin et al. (2009), the rate of recurrence after elective surgery following initial colonoscopy was reported as 0% in all patient groups [23].

Our treatment steps in sigmoid volvulus are towards performing prophylactic surgery in appropriate cases after successful endoscopic detorsion. Regrettably, the patient's acceptance of surgery is at a low rate, and in patients who receive surgical intervention, our priority is to perform the surgery laparoscopically in appropriate cases [30].

No matter which surgical method is preferred, prophylactic surgery is necessitated for the treatment of sigmoid volvulus. The type of surgical intervention depends on various factors such as surgical experience and patient suitability. Surgical timing is at least as important as the intervention. That prolonging the interval increases the risk of recurrence, furthermore morbidity, and mortality.

20.3 Diverticular Disease

Diverticulosis is explained by the presence of the diverticulum and can be asymptomatic or symptomatic. Diverticular disease of the colon is described as clinically significant and symptomatic diverticulosis due to diverticular hemorrhage, diverticulitis, diverticulum-associated segmental colitis, or symptomatic uncomplicated diverticular disease. Diverticular disease of the colon is a leading cause of hospitalization and has significantly increased health care costs in industrialized countries [31, 32]. In this chapter, we will aim to focus on particularly the spot and requirement of prophylactic surgery, in terms of before and after the diverticulitis attack, as well as the presence of symptomatic uncomplicated diverticular disease (SUDD), and segmental colitis associated with diverticular disease (SCAD) will be evaluated.

The prevalence of diverticulosis is age-related while the prevalence at age 60 is less than 20%, it increases to 60% towards age 60 [33, 34]. The lifetime risk of diverticulitis of an individual having diverticulosis was ranged from 10% to 25% [35]. Considering the results based on modern diagnostic approaches such as CT and flexible endoscopy, 5% of patients with diverticulosis have been reported to have diverticulitis [36].

Compared with Asia, diverticular disease is predominantly left-sided in western countries, and right-sided diverticulitis is present in only 1.5% of cases [37].

The diverticular disease also reveals some diversity in age and gender. In female patients, fistula arises more frequently, while in men, bleeding is more common. Older female patients confronted with chronic disease and stricture, younger women present mostly with perforation. While bleeding is at the forefront of older men, younger men frequently present with fistula [38].

Diverticulosis is closely related to intraluminal high-pressure levels, so much so that, the normal intracolonic peak contraction pressure was measured almost 9 times higher than normal individuals, (90 mm/Hg) [39]. With this rising pressure, mucosal herniation occurs through weak spots (vasa recta brevia) in the colon wall and is called acquired or pulsion diverticula.

Abnormal colonic motility is another important predisposing factor in the development of diverticula. It is hypothesized that the increase in intraluminal pressure influences on herniation of

mucosa and submucosa. Besides the studies that the disease may have a neurological basis, the situation is not clear. In published studies on this, deterioration in cholinergic activity can cause asynchronous low-frequency slow waves, which are not related to the action potential [40, 41]. Meanwhile, reports are confirming that hypersensitivity in colon smooth muscles may be the outcome of M3 receptor upregulation due to central effects [42–44].

As a consequence, in a diverticular colon, there is more cholinergic innervation than normal, while there are fewer inhibitory noncholinergic and non-adrenergic nerve activities, which leads to increased intraluminal pressure and segmentation [44].

20.3.1 Classification

Diverticular disease may be evaluated in two headings as symptomatic and asymptomatic. With the recent definitions, symptomatic diverticulitis can be classified as diverticulitis, symptomatic uncomplicated diverticular disease (SUDD), and segmental colitis associated with diverticulosis (SCAD), respectively.

20.3.1.1 Asymptomatic Diverticulosis

Asymptomatic diverticulosis defines the majority of cases while defining the absence of symptoms despite the presence of diverticula. It is frequently identified incidentally in patients undergoing imaging due to other indications [45].

20.3.1.2 Diverticulitis

Diverticulitis is divided mainly into two as clinically acute and chronic course. While acute diverticulitis shows signs and symptoms of inflammation, this situation may be simple, limited to colonic wall and surrounding tissues, or complicated, accompanied by perforation. Chronic diverticulitis can be atypical or recurrent/persistent. Besides, the complex disease can be mentioned as a subgroup, and the malignant diverticulitis status of this group progresses with severe fibrosis, inflammation, obstruction, and fistula formation in which postoperative morbidity and mortality are high [46].

20.3.1.3 Symptomatic Uncomplicated Diverticular Disease

As mentioned above, there have recently been revisions in the evaluation and nomenclature of symptomatic diverticulitis. These involve chronic recurrent diverticulitis, SCAD, and SUDD [47, 48]. SUDD is characterized as chronic diverticulosis with associated chronic abdominal pain in the lack of acute diverticulitis or absolute colitis symptoms [48]. SUDD and irritable bowel syndrome (IBS) may overlap pathophysiologically due to their visceral hypersensitivity, which has been identified by Clemens et al. (2004) in patients with a diverticulum in the sigmoid colon [48, 49].

20.3.1.4 Segmental Colitis Associated with Diverticulosis

The pathogenesis of segmental colitis associated SCAD is inadequately comprehended. The cause may be multifactorial, related to mucosal prolapse, localized ischemia, or fecal stasis. SCAD is characterized by the inflammation of the interdiverticular mucosa without including diverticular orifices, in the presence of multiple diverticula of the sigmoid colon [50, 51]. While patients are usually presented with diarrhea and/or cramping abdominal pain, some of them arise with rectal bleeding [50, 52]. Although the majority of patients respond to medical treatment, approximately one-third of patients encounter relapse within 3 years [53].

20.3.2 Surgical Management

Surgical management of the diverticular disease can be classified as an emergent and elective approach into two main topics in terms of management. Although the acute surgical approach is not our main topic, it is worth mentioning briefly.

In acute patients, the surgical procedure determines and alters the degree of peritoneal contam-

ination (Hinchey Classification) and the patient's stability. Surgical indication in acute disease, the failure of the non-operative approach, the presence of peritonitis with free perforation, and the obstruction related to the disease which could not be resolved with conservative management can be counted. Depending on the degree of fecal contamination and inflammation, the surgical technique can range from Hartman's procedure to primary anastomosis with or without proximal diversion.

Before deciding on the surgical intervention, the most crucial goal is to confirm the diagnosis and to be able to perform the precise procedure for the right patient. Primarily all, patients with complicated diverticulitis should be evaluated in terms of cancer that may lie below [54, 55]. Endoscopic evaluation is essential at this point. In systematic review and meta-analysis performed by Sharma et al. (2014), these rates were 11% and 0.7% in complicated and uncomplicated diverticulitis, respectively [56].

Computed tomography has an important place in evaluating patients. In addition to being able to distinguish between complicated and uncomplicated disease, early CT-guided drainage prevents emergent surgery with complicated diverticulitis, allowing safe elective surgery with reduced mortality and morbidity rates [57].

According to our prior knowledge, while having a complicated or a non-complicated diverticulitis attack was a state that considered for elective colon resection, [58] nowadays there is a shift in this paradigm. In the past, regardless of the number of attacks, while sigmoid colectomy was the first step preference, of the management of the diverticular disease, nowadays it has shifted to a more conservative point in the light of current data and guidelines.

In fact, the conditions that constitute the most important indication for elective surgery are the presence of persistent and chronic symptoms that affect the quality of life. When the literature is evaluated in general, recurrences are detected in patients having abscess and who are treated medically. In particular, the size (5 cm) and the location (pelvic) of the abscess appear to be effective in this circumstance [59]. In this patient group, 5-year recurrence rates were reported between 9.6% and 61% in various single-center cohort studies [60–64]. Although it encounters recurrence after abscess, this can be managed non-operatively [61, 65]. Surgical intervention that is planned to be applied after successful medical treatment in patients with large abscess should be evaluated together with the patient [66].

Recurrence rates in non-operatively treated uncomplicated diverticulitis are between 13% and 33% [67]. In other words, the need for emergent surgery and stoma formation after an improved attack is stated as one in 2000 patients annually [68]. Besides, in a retrospective study, 80%–90% of patients who need urgent surgical intervention has been shown to have this need during index attack, [69] and elective colectomy does not significantly reduce the need for emergent surgery [70–72]. As the number of attacks increases, the probability of relapse increases each time [73, 74]. After the first episode of diverticulitis, the rate is 8.7%, meanwhile, the rate increases to 36% after the third episode [75]. At this point, the patient may be disturbed by repeated attacks and ongoing medical treatment as well as persistent symptoms and prefer elective surgery. When making an elective surgery decision, the risks, morbidity, and ostomy requirements of this intervention should be evaluated simultaneously with the patient's preference [69, 76–78].

In another arm of the DIRECT trial, it was pointed out that elective surgery is cost-effective in patients with recurrent diverticulitis as well as improving the quality of life [79]. A similar result stated that as a result of the cost-efficacy analysis performed by Salem et al. (2004), surgery performed after the fourth episode resulted in less death as well as being cost-effective for both young and old patients [80].

Another notable intervention change has become fore in patients with diverticulitis at a young age under 50. In this patient group, elective surgery after the first episode was recommended in the past literature [81, 82]. Although young patients comprise an increas-

ingly considerable proportion of all patients diagnosed and have an increased risk of recurrence [83, 84], there is limited evidence that shows a worse course than older patients if treated non-operatively [85]. In the retrospective cohort study in which 14,124 patients were included, the readmission rates of the younger patients who were applied non-operative approach after the first diverticulitis attack were higher, and the need for urgent surgery was similar compared to the elderly patients [86]. When evaluated with guidelines, elective colectomy is not recommended in patients having diverticulitis episodes [87].

It is controversial to recommend elective colectomy after successful medical treatment of diverticulitis episode in immunocompromised patients. Compared to the regular population, immunosuppressive patients have higher rates of having acute diverticulitis, needing emergency surgery, and mortality after emergency surgery [88, 89]. Although there may be a necessity for emergent surgery due to delayed or atypical presentation in this patient group, those who complete the medical treatment foresee risks at the point of elective surgery compared to the regular population. In a retrospective study evaluating patients who underwent elective sigmoidectomy for diverticulitis, the morbidity and wound dehiscence rates were detected significantly higher in immunocompromised patients [90]. Considering recurrence after episodes, immunocompromised and immunocompetent patients have similar proportions, therefore, the patient's form of treatment should be individualized, taking into account the additional comorbidities of the immunocompromised patient after an uncomplicated diverticulitis attack [91].

In the 2014 ASCRS recommendations, they suggested maintaining a low threshold for colectomy in transplant patients, [59] while in a single-center retrospective review, they stated that 12 patients with renal transplant and 93 patients with immunocompetent were successfully treated medically after diverticulitis and their recurrence rates were similar in their follow-up for 33 and 41 months, respectively [92]. Some other series state that, undergoing transplant and patients on steroids, recommend colectomy due to immune-suppresion after one episode of diverticulitis and usually during the index admission [93]. Since surgery is associated with high morbidity and mortality in patients with end-stage renal failure, colectomy should be reserved for patients whose surgical approach is inevitable.

Whether open or laparoscopic, the surgical technique should cover the healthy margins of the colon in elective colectomy. This requires resection of the entire sigmoid colon affected by diverticulitis up to the proximal rectum (sacral promontory). Elective surgery should be performed for a period of 6 weeks or more, if possible so that infection and inflammation are resolved. Therefore, early surgery is the reason for longer hospitalization and high conversion rates [94]. In some cases, if anastomosis will not be performed due to inflammation through the proximal rectum, an extensive rectum resection may be required by going below the sacral promontory. Paying attention to these issues will decrease the recurrence rate that may occur in the forthcoming years. Current studies reveal that colon-colonic anastomoses cause marked recurrence [95, 96]. Likewise, if resection of the entire diverticular segment at the border of the proximal colon is not feasible, the anastomosis must be performed in the area where there is definitely no inflammation and diverticula, in that way the risk of an anastomosis leak is reduced. Although splenic flexure mobilization has not been demonstrated to affect a decrease in perioperative morbidity and recurrence, full mobilization of the descending column is recommended for a tension-free anastomosis.

In Sigma trial, short-term open and laparoscopic approaches were compared and found less pain, improved quality of life, less blood loss, and less hospitalization in laparoscopic resection despite longer surgery time [97]. In another randomized trial, both surgical approaches did not find any difference in terms of incisional hernia, quality of life, and long-term complications in the long term; moreover, it was stated that laparoscopic surgery had a cosmetic benefit in the long-term follow-up [98]. In a meta-analysis of 25 randomized controlled trials, it showed that the laparoscopic approach is superior in terms of

short-term results in colorectal surgery with any indication [99]. As a result, if an expert surgeon is present and a colorectal resection will be performed for elective diverticulitis, a laparoscopic approach is recommended [59].

While prophylactic surgery was recommended after 1–2 episodes of diverticulitis, nowadays elective prophylactic surgery is recommended in limited cases by indicating the suitability of management with a conservative method in their recurrences. But the principles of surgical approach have not changed. Surgery priorities are control of infection, reducing morbidity, and improving quality of life furthermore, laparoscopic techniques should be favored if there are proper conditions in the choice of surgical technique.

Our approach to diverticulitis is in favor of elective prophylactic surgery in patients with symptomatic but presenting no radiological symptoms (ongoing diverticulitis) and high recurrence frequency as well as a personalized approach.

In the light of recent literature, the elective prophylactic surgical approach of diverticular disease should be individualized, taking into account circumstances such as the patient's age, immune status, additional diseases, as well as the patient's preferences.

20.4 Ulcerative Colitis

Ulcerative colitis (UC) is a chronic inflammatory disease with relapsing and remitting episodes, limited to the mucosal layer of the colon. Although the involvement habitually characterized in the rectum, this involvement may progress towards the proximal segments of the colon and classified as according to the involved portion of the colon (ulcerative proctitis, ulcerative proctosigmoiditis, left-sided colitis, extensive colitis) [100, 101].

In the last 20–30 years, the incidence of UC has increased 2- to tenfold due to possible environmental factors, which cannot be explained by genetic factors [102, 103]. The incidence of UC is reported in North America as 2.2–19.2 cases per 100,000 person-years. UC ordinarily presents within two peaks between the ages of 15–30 and 50–80 years [104, 105]. UC is more common in the male sex [106]. Although smoking does not increase the risk in UC, it is stated in studies that it reduces the risk of disease [107, 108]. Increased dietary intake of animal fat and polyunsaturated fatty acids have been associated with increased UC, and sleep deprivation also causes similar results [109–111]. The use of some drugs affects UC at various rates. For instance, while the risk of UC slightly increases in the NSAIDs, the risk is elevated in the consumption of oral contraceptives [112, 113].

The diagnosis of ulcerative colitis is based on the presence of chronic diarrhea for more than 4 weeks and evidence of active inflammation on endoscopy and chronic changes on biopsy. Since these features are not specific for ulcerative colitis, establishing the diagnosis also requires the exclusion of other causes of colitis by history, laboratory studies, and by biopsies of the colon obtained on endoscopy.

Proctosigmoidoscopy, flexible sigmoidoscopy, and colonoscopy are important tools for evaluating the bowel and for confirming the presence of UC. Besides, endoscopic evaluation is critical in terms of both making differential diagnosis from other inflammatory bowel diseases and taking biopsies that are necessary to make a pathological diagnosis.

20.4.1 Treatment

Except for the emergency surgery requirement of UC, elective surgery is required in selected patient groups. These patient groups include those with chronic persistent symptoms despite appropriate medical treatment, and patients having long-standing illness and/or dysplastic/adenomatous polyps.

Patients with UC have an increased risk of colorectal cancer. The duration, expanse, and activity of colitis are the most critical risk factors [114–117]. This group of patients is the most crucial part of prophylactic surgery. While the risk of cumulative cancer in patients with UC is

4% in the first 10-year period with symptoms, this risk increases more markedly in the following years and reaches 40–48% after 25 years of symptomatic colitis [118–122].

Four types of surgery can be mentioned to be frequently performed. These are restorative proctocolectomy with ileal pouch-anal anastomosis (RPC-IPAA), total abdominal colectomy with ileorectal anastomosis (TAC-IRA), total abdominal colectomy with end ileostomy, and total proctocolectomy with end ileostomy, respectively. These four techniques can be performed open or minimally invasive (laparoscopic, single port, robotic) methods [123–125]. Recently, transanal ileal pouch-anal anastomosis (Ta-IPAA) has also been introduced as a new minimally invasive approach [126].

RPC-IPAA is the surgery type that is frequently preferred in elective surgery. In this technique, the entire colon and rectum are removed, and the prepared ileal pouch anastomosis is applied to the anal region where the sphincters are also preserved. The process can be performed in single stage or can be completed up to three stages, furthermore in the IPAA, hand-sewn or stapled anastomosis technique can be preferred. Outstanding fecal continence and bowel functions are frequently provided following surgery. This type of surgery may not be suitable for young women who desire future fecundity due to pelvic adhesions, thereby TAC-IRA could be the right decision until completing the desire for future pregnancy. Patients who prefer TAC-IRA should be included in the close endoscopic surveillance program. The significant reason for this issue is the remaining rectum, and cancer development in the first 20 years was reported as 6% and 16% in 30 years. In a retrospective study involving 86 patients, 53% of patients who underwent TAC-IRA underwent additional rectal resection. It has been stated that 17% of them are caused by rectal dysplasia, 8% cancer, and 28% refractory proctitis [127]. Considering that the majority of patients with UC are young, it is obvious that close follow-up is essential. Patients with significant comorbidity, and having poor anal sphincter function, total proctocolectomy with end ileostomy will be the right option in terms of surgical technique in elderly patients. The end ileostomy is permanent and can be constructed in a continent (Kock) or incontinent (Brooke) fashion.

The overall aim of this patient group is to reduce the risk with prophylactic surgery and surveillance programs [128]. Although IPAA is surgically successful in patients with UC, the recommendation for prophylactic surgery is controversial [121, 129, 130]. Endoscopic surveillance and biopsies taken from the anal canal mucosa are critical in the detection of cancer that may arise from residual rectal tissue.

We frequently perform RPC-IPAA, individually, taking into account both comorbid diseases and preferences. Endoscopic surveillance is a critical cornerstone in patients with IRA. Although the risk of cancer is lower in IPAA than IRA, in IPAA, endoscopic surveillance is controversial [131]; we do prefer endoscopic surveillance in our patients who have undergone IPAA.

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Prophylactic Adrenalectomy

21

Mehmet Haciyanli, Emine Ozlem Gur, and Selda Gucek Haciyanli

21.1 Introduction

Over the past decades, widespread use of screening, genetic testing and innovations in surgical techniques have resulted in early diagnosis and identification of high risk patients for cancer development and hence resulted in improved overall survival and clinical outcomes across many cancer types. As a consequence, "Prophylactic Surgery" concept emerged. Prophylactic surgery or preventive surgery is defined as "surgery to remove an organ gland that shows no signs of cancer, in an attempt to prevent development of cancer of that organ or gland" in National Cancer Institute (NCI) Dictionary of Cancer Term [1].

To apply a prophylactic surgery to an organ or gland, the balance between the oncological benefit and quality of life versus the risk of operation and cost efficiency should be considered. Prophylactic thyroidectomy for gene carriers of Multiple Endocrine Neoplasia (MEN) type 2 (before medullary thyroid cancer (MTC) develop) has been well-defined example of prophylactic surgery in endocrine surgery field. However, the data about the indications of the prophylactic surgery of the adrenal glands is very limited in the literature. Moreover, currently there is no place for "prophylactic adrenalectomy" similar to that of "prophylactic thyroidectomy" in classical manner. When the term "prophylactic adrenalectomy" is searched in PubMed, only few anecdotal reports can be found. The reason is that for most hereditary syndromes causing adrenal tumors, surgeons wait for lesions to develop before to resect the adrenal because the risk is not worth the benefit, also delay will not cause same issue as in MTC. The existence of two adrenal glands and absence of ideal substitute for adrenal hormones also increases the complexity of the issue.

Adrenalectomy for large adrenal tumors that have high risk for cancer is not considered "prophylactic"; it is considered "diagnostic" and possibly "therapeutic" if it turns out to be a cancer.

However, in the area of endocrine disease, especially in adrenal disease, risk reduction surgery can be used to prevent the development of severe conditions. Instead of total adrenalectomy, function-preserving, cortical sparing adrenalectomies (CSA) have been used in certain circumstances, especially in some hereditary bilateral pheochromocytomas (PCC) to "prevent" adrenal insufficiency which is a debilitating condition, require lifelong steroid replacement and are associated with long-term morbidity and even death.

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So CSA can be a non-classical example of preventive surgery (which prevents functional loss while treating the tumor) which has been increasingly performed in PCC patients with mutations of RET or Von Hippel Lindau (VHL), because of the low risk of malignancy (<5%) and high risk of bilaterality (50%) [2, 3].

Another two examples for preventive adrenalectomy might be the surgery for patients with adrenal incidentalomas (AI) and autonomous cortisol secretion (ACS). Patients with ACS have an increasing risk of developing severe cortisol-related comorbidities such as atherosclerosis, hypertension, diabetes, cardiovascular events and related mortality, bone fractures, and infectious diseases. Considering the increasing number of patients with this condition, it is important to identify high risk patients to perform adrenalectomy to prevent those complications.

Under the highlights of the current literature, we will discuss the current status of preventive and diagnostic surgery for adrenal lesions.

21.2 History

When "prophylactic" or "preventive" "adrenalectomy" terms are used as a search term in PubMed, only few anecdotal reports were encountered. Prophylactic bilateral adrenalectomy (± oophorectomy) was used to control the disease in patients having advanced breast cancer in 1960s [4, 5]. However with the advances in medical treatment with pharmaceuticals and the inadvertent results of such a surgery, it has not been used anymore for such an indication.

A group of researchers proposed prophylactic bilateral adrenalectomy as an option for patients affected by Congenital Adrenal Hyperplasia (CAH) and performed the operation in a few patients having a double null mutation of the CYP21 gene as a part of an approved research protocol [6, 7]. They concluded that prophylactic adrenalectomy in young children with such mutations should remain experimental [7].

Up to 40% of patients with PCC have disease-specific germline mutations and the disease is hereditary. Of 60% of the remaining sporadic patients, at least 1/3 have somatic mutation in predisposing genes [8].

MEN 2, VHL syndrome, Neurofibromatosis Type 1 (NF-1) (=von Recklinghausen's Disease—VRD) are well-known examples of genetic syndromes associated with PCC.

With the advances in genetic analysis, the carriers can be easily identified and prophylactic thyroidectomy concept has been a well-established approach for MEN2 to prevent the development of medullary thyroid cancer which is an aggressive disease. However, prophylactic adrenalectomy concept has never been well established for those carriers before the development of one-sided disease. Since PCC is bilateral almost in 50% of the patients with MEN2 and VHL, some suggested total bilateral adrenalectomy in those patients including the patients with unilateral PCC to reduce the risk of recurrence and eliminate the risk of malignancy in the future. But it has been detected that malignancy is uncommon in both VHL and MEN2, and the complications of bilateral total adrenalectomy are disastrous, patients need lifelong steroid and hospital dependence. To avoid from such severe complications, there has been an increasing trend to preserve adrenal tissue in patients with MEN 2, VHL, and NF-1. CSA can be classified as a preventive surgery which prevents the lifelong intrinsic steroid insufficiency.

21.3 PCC-Heritable PCC

PCCs are rare endocrine tumors originating from chromaffin cells in the adrenal medulla and secrete excess catecholamines such as epinephrine, norepinephrine, dopamine and/or their metabolites including metanephrine, normetanephrine, and 3-methoxytyramine, respectively [9, 10]. The annual incidence of PCCs in the United States is estimated about 500–1600 cases per year and the prevalence of them is estimated to be 1–2500 and 1–6500 [11]. The patients are typically symptomatic in their fourth or fifth decade of life, with an equal sex distribution [12].

The classical presentation of the disease consists of episodic flushing, diaphoresis, headaches,

and hypertension, in approximately 40% of patients [13]. Almost 10% of patients have bilateral tumors [14]. PCCs comprise about 4–8% of all adrenal incidentalomas, and about 21.1–57.6% of all PCCs are discovered incidentally on imaging [15, 16]. About 10% of all PCCs are malignant, but the likelihood of malignancy depends on the presence of certain germline mutations (SDHB in particular) [17, 18].

The contribution of genetic predisposition either from a familial predisposition or de novo mutation [8, 19] increased to 40% with the discovery of new susceptibility genes. Patients suspected to have PCC should first undergo biochemical testing of catecholamines and their metabolites to establish or rule out the diagnosis. After the biochemical diagnosis has been reached, genetic testing must be completed. Then anatomical and functional imaging should be performed, before surgery. The extent of adrenalectomy and type of surgery is individualized based on multiple factors such as the results of genetic testing, the size and bilaterality of the tumor, the likelihood of malignancy, body mass index of the patients, and the experience of the surgeon.

21.3.1 Biochemical Studies

The biochemical diagnosis of PCCs depends on the measurement of catecholamines and their metabolites (metanephrine and normetanephrine) both in serum and urine. The metabolites are superior in diagnosis to circulating catecholamines [20]. The most accurate biomarker for diagnosis is a plasma free metanephrine (a sensitivity of 94%, specificity of 93%) [21]. Endocrine Society Practice Guidelines recommended for the initial workup for PCC either plasma free or 24-h urinary fractionated metanephrines [22]. False-positive results may be due to a drug interference (tricyclic antidepressants, acetaminophen, sulfasalazine, phenoxybenzamine, sotalol, labetalol, alpha-methyldopa, monoamine oxidase inhibitors, sympathomimetics, buspirone, cocaine, and levodopa) or laboratory errors [9, 23]. Repeat testing is recommended after the cessation of medications.

21.3.2 Genetic Background

Since up to 40% of PCCs may have genetic predisposition, all patients with a diagnosis of PCC should be referred for genetic testing [24, 25]. The mutations determine the pathophysiology and biologic behavior of PCC and the management of those patient and their affected members of family are dictated by those inherited mutations. More than 20 gene mutations have been detected in patients with PCC and paraganglioma (PGL) which lead tumor development as either a germline (inherited) or somatic mutation (non-inherited) [8, 26, 27].

Patients with PCC and PGL with these mutations can be divided into three groups according to the cancer genome map (Table 21.1) [28].

PCC and PGL related to mutations in SDHx subunits are often multiple, aggressive and metastatic tumors compared to those originating from other mutations, especially cluster 2 mutations [29]. More specifically, SDHB mutation has increased risk of malignancy [30].

About 95–100% of patients with VHL syndrome are related to the mutation in the VHL tumor suppressor gene. The tumors with mutations in cluster 1 have a noradrenergic biochemical phenotype. They produce norepinephrine and dopamine, not epinephrine [31].

Table 21.1 Genetic mutations in PCC and PGL according to cancer genome

Cluster 1 Pseudohypoxic Krebs cycle-related genes	Cluster 2 Kinase signaling-related genes	Cluster 3 Wnt Signaling-related genes
SDHx SDHA, SDHB, SDHC, SDHD SDHAF2 FH MDH2 IDH1	RET	Somatic
VHL/EPAS1 VHL PHD1 (EGLN1/2) HIF2A/EPAS1/2	NF 1	
	HRAS	
	TMEM127	
	MAX	

The most common hereditary syndrome in patients with cluster 2 mutations is MEN2 and the majority adrenergic biochemical phenotype (excess epinephrine production). Norepinephrine may increase or at normal levels in them [31]. Most PCCs associated with those mutations are benign but have a high rate of multifocality [32].

Those tumors with cluster 3 type mutations are related to aggressive features [28].

The germline mutation and biochemical phenotype of this category is unknown [31–33].

In general, the risk of metastatic disease in decreasing order is as follows: mutations associated with cluster 1 mutations, cluster 3, cluster 2 [29].

21.4 Genetic Syndromes Associated with PCC AND PGL

21.4.1 MEN 2 Syndrome

MEN2 syndromes are autosomal dominant diseases and caused by mutations in the RET proto-oncogene. Medullary thyroid cancer develops in almost 100% of patients with MEN2 (A and B), whereas PCC in 50% of patients with MEN2 (both in A and in B) [34].

In MEN syndromes, the tumor is often localized in the adrenal medulla and paraganglioma (PGL) is very rare [29]. PCCs in this syndrome make up 5% of all PCCs [35]. Bilateral adrenal involvement occurs in 50–60% [2, 35]. It can be synchronous or metachronous. Its biochemical phenotype is adrenergic [36].

Metastatic disease is quite rare (≤1%) [9]. Hyperparathyroidism is another component of MEN2A syndrome, whereas neuromas and marfanoid habits can be seen in patients with MEN2B. PCC should be treated prior to surgery for other components of the syndrome.

21.4.2 VHL Syndrome

VHL Syndrome is an autosomal dominant disease caused by the germline mutation in the VHL tumor suppressor gene. Cerebellar and spinal hemangioblastomas, retinal hemangioma, renal cysts, renal carcinoma of clear cell type, pancreatic neuroendocrine tumors, cysts and cystadenomas, PPGLs, cystadenomas in gonads, benign asymptomatic lung and liver lesions can be seen in this syndrome [2].

PCC and rarely PGLs are seen in about 20% of patients with a young age of onset. Tumors are usually of adrenal origin and produce norepinephrine. Twenty percent of PCCs in this syndrome are bilateral [37, 38] and metastatic disease is rare [5%].

21.4.3 NF1 Syndrome

NF1 is an autosomal dominant disease caused by mutation in the NF1 gene and characterized by multiple neuromas and peripheral nerve sheath malignant tumors (15%) [39]. In addition, café au lait spots, freckles in the axilla and inguinal areas, malignant glioma, bone lesions, gastrointestinal stromal tumors, and PCC may occur [40, 41].

PCC develops in 1–5% of patients with NF-1 [22]. They constitute 1% of all patients with PCC [40]. All patients with PCC and NF1 exhibit cutaneous manifestations on physical examination. Tumors are bilateral in 20% of cases [42]. Approximately 7–12% of them are metastatic [22].

21.4.4 Hereditary PGL Syndromes Type 1–5 (SDH Complex)

The PGL syndrome arises from mutations on genes encoding the enzyme succinate dehydrogenase (SDH) with autosomal dominant inheritance. These syndromes are more often associated with PGL. Head and neck PGLs are common. PCCs are seen rarely. Malignancy rate is higher in SDHB mutations and 30–70% malignancy has been reported; in other types, malignancy rate is low [22].

21.5 Genetic Testing

All current guidelines worldwide recommend the genetic testing to all patients having PCC and PGL [9, 24, 43] regardless of family history or age.

Next generation sequencing (NGS) is currently the gold standard for genetic testing. A consensus statement on NGS testing for patients with inherited PCC explains the variety of associated genes and standardizes reporting [44]. With NGS, it can be possible to test the most common predisposing genes (SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, VHL EGLN1, FH, KIF1B, MAX, MEN1, NF1, and RET) accurately. The genes typically are sequenced and evaluated for duplications and deletions of exon. Due to the complexity of interpreting the results, the patients should be offered to have a genetic consultation before testing.

Genetic testing enables the surgeon to individualize surgical approaches and decide the extent of adrenalectomy. Patients with an SDHB mutation which typically represents more aggressive disease were more likely to be operated via an open surgery and total adrenalectomy even in bilateral cases [45]. On the other hand, approximately 50% of MEN2 and 20% of VHL patients have bilateral PCC and since the metastatic diseases are quite low in those patients identified genetically, cortical sparing adrenalectomy (CSA) which will be discussed further in this chapter should be considered to prevent adrenal insufficiency.

21.6 Imaging

After biochemical confirmation of PCC, imaging of tumor with either computed tomography (CT) and/or magnetic resonance imaging (MRI) is essential for surgical planning. Both of those techniques have similar high sensitivity and specificity (90–100 and 70–80% respectively) for identifying adrenal tumors [9].

PCC will measure more than ten Hounsfield on non-contrasted CT images and have marked enhancement on arterial phase images as well as delayed venous washout on contrasted CT images [46, 47]. Cystic changes, intratumoral hemorrhage, central necrosis, and internal calcifications may be detected as the lesion increases in size (Fig. 21.1). MRI shows T2 enhancement with contrast (light bulb sign). The adrenal mass may also appear heterogenous due to central necrosis, cystic changes, or hemorrhage [47] (Fig. 21.2).

Bilateral lesions on CT/MRI must raise suspicion for a hereditary disease. Functional imaging can be used in such a situation or when a metastatic disease is suspected. Functional imaging methods, which use radiotracers dependent on glucose metabolism, catecholamine secretion and metabolism, or tumor somatostatin receptor existence aid in the detection of additional smaller, functioning lesions in the same or contralateral gland which is critical for decision on the extent of the surgery. So functional imaging should be performed before decision on cortical sparing adrenalectomy in hereditary or bilateral PCC.

123I-metaiodobenzylguanidine (MIBG) is an effective functional imaging method with a sensitivity of around 90% and specificity of 70–100% for isolated PCC [48, 49]. However, its sensitivity decreases with extra-adrenal, metastatic, and

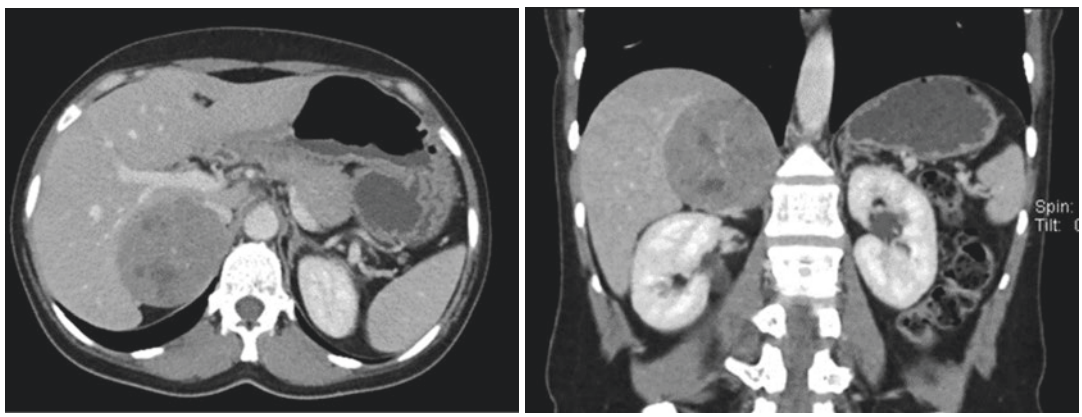

Fig. 21.1 The hypodense solid mass in right adrenal gland in portal venous phase axial and coronal computed tomography images

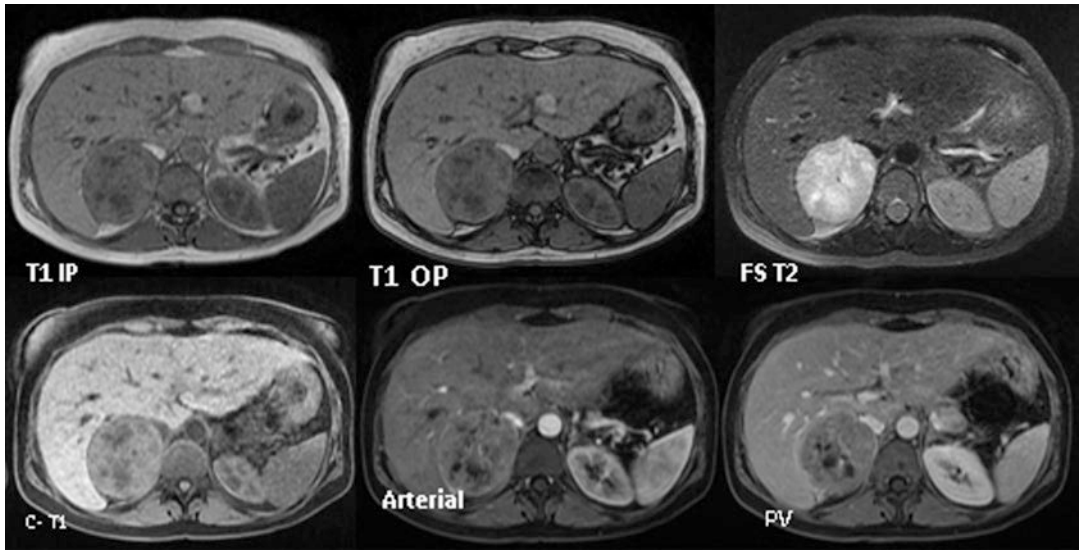

Fig. 21.2 Right adrenal mass in MRI images. *OP* out of phase, *IP* in phase, *FS T2* fat sat T2, *PV* portal venous phase

recurrent PCCs [48–50]. It may be useful in highly selected cases such as for patients with negative genetic screens and those with bilateral adrenal tumors, both of which have suspicious features for PCC based on CT/MRI findings.

Positron emission tomography (PET)/CT using 18F-fluordeoxyglucose (18F-FDG), an 18F-3,4-dihydroxyphenylalanine (18F-DOPA) has been evaluated in patients with PCC but found that 18F-FDA was superior to 18F-DOPA and 123I-MIBG in localizing metastatic disease [50]. However, 18F-FDA is available only at the United States. 18F-FDG PET/CT has a high sensitivity for SDHx and VHL-related PCC, but 18F-DOPA PET/CT has higher performance in sporadic as well as in MEN2 and NF1-related PCC and is the more appropriate functional imaging choice for those patients [50, 51].

PCCs express somatostatin receptors like many other neuroendocrine tumors. There is an increasing report demonstrating the superiority of (68Ga)-DOTATATE PET/CT in the detection of PCC compared with other functional imaging methods [52]. (68Ga)-DOTATATE PET/CT may become the primary functional imaging method for PCCs when indicated [22].

21.6.1 Diagnosis of Hereditary PCC

PCC is detected during the genetic diagnosis or during the follow-up of mutation carriers who are diagnosed by familial screening. The steps of diagnosis in hereditary cases are identical those of sporadic cases, but the option of CSA is more obvious in mutation carriers because the PCC is generally smaller.

When PCC is present at the genetic diagnosis after the biochemical diagnosis of PCC, conventional imaging (CT/MRI) is performed to determine the size of the PCC, the number of lesions, and the possibility of performing a CSA. The functional imaging with 18F-FDOPA or (68Ga)-DOTATATE PET/CT is important in hereditary PCC for the decision process for CSA [22, 53].

In mutation carriers (no PCC at the time of genetic diagnosis), there is no consensus on the diagnosis of PCC in those patients but the follow-up is necessary for the option of CSA.

Symptoms and signs of catecholamine oversecretion are usually absent in mutation carriers but metanephrines may increase progressively in time. Monitorization of normetanephrines and metanephrines both in plasma and urine annually

should be done annually throughout the patient's lifetime.

The role of imaging during the follow-up of those patients is not known. The imaging before biochemical diagnosis may aid in the detection of a small and non-secreting PCC [54]. This screening would help in decision for an early surgery and CSA. The use of MRI rather than CT in childhood may be considered to avoid radiation exposure. Some suggest adrenal MRI every 3–5 years and there is likely no place for functional imaging in this setting of surveillance [54].

21.7 Preoperative Considerations

The presurgical management of partial adrenalectomy does not differ than the classical adrenalectomy for PCC. The Endocrine Society guidelines recommend preoperative use of α-blockers followed by β-blockers for the maintenance of normal blood pressure levels [9]. Some have reported successful results with preoperative use of calcium channel blockers, but the major factor in the treatment is the experience of the surgeon and anesthesiologist in the management of PCC [53].

21.7.1 Candidates for CSA

The patients at risk for adrenal insufficiency are those necessitating synchronous or metachronous bilateral adrenalectomy. The ideal candidates are patients with hereditary PCC with VHL, MEN2, and NF-1 syndromes, and with small tumors on the remaining adrenal who had a previous contralateral total adrenalectomy.

Patients having synchronous or metachronous sporadic bilateral PCCs may be another group of candidates. Another group of patients candidate for CSA are those with a single gland, i.e., patients who had one of their adrenal glands resected due to trauma or renal surgery. Partial adrenalectomy has been performed for some patients having Conn's disease and adrenal Cushing disease but those two are out of context of this chapter.

21.7.2 CSA Technical Points and Results

The three questions related with CSA to be answered are:

1. Does it have a very low risk of malignancy?
2. Does it have an acceptable risk of recurrence?
3. Does it maintain normal adrenal cortical function?

The first modern clinical use of partial adrenalectomy (open, bilateral) was reported by van Heerden et al. (1985) from Mayo Clinic for the treatment of bilateral PCCs in a pilot patient with MEN 2A syndrome [55].The first transabdominal laparoscopic adrenalectomy was performed in 1992 [56]. Laparoscopic retroperitoneal adrenalectomy was described by Mercan et al. (1995) and proposed as a good alternative in selected cases [57, 58]. In 1996, laparoscopic partial adrenalectomy method was reported by Walsz [59].

Surgical techniques for adrenalectomy include both open and minimally invasive (laparoscopic or robotic) approaches. When operating a patient with PCC, early ligation of the adrenal vein, and minimal manipulation of the tumor to prevent release of catecholamines and tumor rupture are the key principals. Minimally invasive adrenalectomy is the preferred operation for PCCs via with either the laparascopic transabdominal adrenalectomy (TA) or posterior retroperitoneoscopic adrenalectomy (PRA) [60–62] which depends on surgeon's experiences, as well as factors such as patients' body mass index, anatomy, tumor characteristics (size and location), and history of prior abdominal or retroperitoneal procedures.

Both approaches have different advantages: TA approach can be used in larger tumors (>6 cm) since the working space is satisfactory and it is easy to convert to open if necessary. It can be performed in patients with prior upper abdominal surgery but adhesions may be problematic. On the other hand, the PRA approach provides direct access to the adrenal gland, without the need for mobilization or adhesiolysis. Another advantage

of PRA is the ability to perform bilateral adrenalectomy without repositioning the patient.

Robotic adrenalectomy, using both TA and PRA approaches, has been described for PCC [63, 64] having advantages on surgeons perspective.

Open transabdominal adrenalectomy is chosen for patients having suspiciously malignant/invasive PCC or having large tumors at risk for rupture. Furthermore, open adrenalectomy should be considered in patients with SDHB, TMEM127, or FH germline mutations, since these mutations are associated with a higher risk of malignancy and recurrence compared with germline mutations in NF1, RET, or VHL [65].

Preserving the healthy cortical tissue by means of partial adrenalectomy has evolved to maintain the adrenal cortical functions and to keep patients away from the adrenal insufficiency. Many different nomenclatures have been used for the approach such as "partial," "subtotal," "adrenal−/organ−/cortical-preserving," and "adrenal−/organ−/cortical-sparing" adrenalectomy. However, intraoperative discrimination between the medulla and the cortex is impossible intraoperatively.

The volume of residual adrenal tissue needed to preserve a functioning gland is one of the challenging issue in partial adrenalectomy. Preservation of at least 15–30% of adrenal tissue during bilateral subtotal adrenalectomy is necessary for normal function [66]. The remaining adrenal tissue must be more than 30% of the gland if only one side adrenal gland left in situ [67]. Although PCC must have a low risk for malignancy, the tumor should be resected with a rim of healthy cortical tissue (3 mm), instead of enucleation [68]. The guideline by The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) recommended the intraoperative laparoscopic ultrasound in partial adrenalectomy to ensure a clear distinction between tumor and normal tissue [69]. The use of indocyanine green (ICG) fluorescence imaging in partial adrenalectomy is helpful in guiding the extent of resection for the confirmation of remnant viability [70].

Ligation of adrenal vein in CSA is another controversial point. Currently several comparative studies suggested that no difference has been observed in steroid dependence between patients with preserved or ligated adrenal vein [71, 72]. Another issue is the preservation of arterial blood supply to the gland. The mobilization of the gland to be preserved from retroperitoneum has not been recommended in order to ensure adequate blood supply [73].

The outcomes of partial adrenalectomies are confusing in the literature. Patients with MEN 2 who undergo CSA have a 3% risk of ipsilateral recurrence compared to 2% of total adrenalectomy at 10 years. The rate of steroid dependency has been reported up to 43% [37]. However, the results of CSA for patients with VHL is encouraging: Benhammou et al. (2010) reported 11% of patients developed recurrence within the ipsilateral adrenal gland remnant and 11% of patients developed a recurrent PCC within the contralateral adrenal gland requiring a partial adrenalectomy and only 11% of patients became steroid dependent and no patients developed metastatic disease [74].

Currently, the indications for CSA are increasing and patients with bilateral benign familial PCCs with VHL, MEN2, and NF-1 syndrome seem to be ideal candidates. This approach has been demonstrated to prevent postoperative adrenal insufficiency in up to 90% of patients [53, 68], although the exact amount of remnant adrenal gland required is unknown.

21.8 Autonomic Cortisol Hypersecretion (Subclinical Cushing's Syndrome)

Autonomous cortisol secretion (ACS) without specific signs and symptoms of Cushing's syndrome is termed subclinical Cushing's syndrome (SCS). Increasing use of abdominal imaging modalities for various reasons has also led to the increasing detection of adrenal incidentalomas (AI) and biochemical evaluation of those patients revealed hypercortisolism.

Different terminology for the phenomenon has been used including "Subclinical Cushing's syndrome," "Subclinical Hypercortisolism," and "Subclinical Autonomous Glucocorticoid Hypersecretion," "Dysregulated hypercortisolism," and "Preclinical Cushing's Syndrome." We are going to use ACS in our chapter.

ACS appeared as the most common functional abnormality in AI patients. Almost 5–20% of adrenal incidentalomas exhibit autonomous cortisol hypersecretion (ACS) subclinically [75]. The optimal management of patients with ACS has not been clarified yet. It is known that significant comorbidities are associated with ACS, and some improvement in associated comorbidities after adrenalectomy have been reported [76, 77]. So we discuss the surgery for ACS in the context of "prophylactic adrenalectomy" which may have a role to prevent the development of hypercortisolism-associated comorbidities.

21.9 Components of ACS

1. Abdominal imaging revealing an adrenal mass
2. Hypercortisolism on biochemical evaluation
3. No classic clinical signs of overt Cushing's syndrome [78]

21.10 Diagnosis

The first screening biochemical test is 1 mg (low dose) overnight dexamethasone suppression test (DST) [78–82]. If oral DST dos not suppress the cortisol secretion, initial diagnosis of Cushing syndrome is reached. A plasma If oral DST dos not suppress the cortisol secretion, initial diagnosis of Cushing syndrome is reached. A plasma cortisol level after low dose DST less than 1,8 mg/dL excludes ACS; however, the cutoff value of cortisol after the DST test changes between several guidelines [79, 80, 83]. Most of guidelines accept 1.8–5.0 mg/dL cortisol level after low dose DST is intermediate group to diagnose ACS. Although more than 5 mg/dL cortisol level is diagnostic for ACS, NIH, AACE/AAES, AME, and ESE recommend additional biochemical tests in those patients for differential diagnosis.

The secondary screening tests that were recommended to show excess cortisol secretion are late-night salivary cortisol (LNSC) and urinary free cortisol (UFC) [83, 84]. LNSC is a diagnostic test for Cushing's syndrome. LNSC is an easier test for the patients because they can collect the samples at home. On the other hand, LNSC test results can be dependent to the patients' sleeping rhythm at the night for the Cushing's syndrome. LNSC has a conjunction with low dose DST for the ACS diagnosis. The sensitivity and specificity of LNSC test for ACS are more than 80% if it has been used with low dose DST [85]. UFC is also effected by a lot of parameters such as chronic anxiety, depression, obesity, and high fluid intake [86]. As with LNSC, a normal UFC does not exclude ACS [87].

The imaging findings are discussed in detail under the heading of incidentaloma in this chapter.

21.10.1 Clinical Presentation

The majority of ACS patients has not any evident clinical symptoms but hypertension, glucose intolerance, and bone mineral changings can be associated with the syndrome.

About 41–92% of patients with ACS have a mild to moderate hypertension [88]. It has also been showed in a 15-year follow-up study that ACS patients have increased cardiovascular morbidity (43% vs. 8.8%, $p < 0.005$) and mortality (22.6% vs. 2.5%, $p < 0.02$) compared to nonfunctional adrenal tumor patients [89, 90]. Impaired glucose tolerance or diabetes has been detected to occur in 10–69% of patients with ACS [91]. Both of the bone lose as trabecular and cortical have been showed in ACS patients [92, 93]. A meta-analysis showed that the prevalence of bone fracture is 63.6% in ACS patients [94].

21.10.2 Surgical Treatment

Two main treatment options for ACS are surveillance/medical management and surgery. Nonoperative management includes surveillance and medical management of excess

cortisol-associated comorbidities if it is necessary. Since ACS is not accepted as a precursor of Cushing's syndrome, whether those patients should undergo adrenalectomy is a matter of debate.

In a meta-analysis of patients with ACS, adrenalectomy resulted in improvement only in hypertension and diabetes when compared with the medically managed ACS patients [95]. Another review showed improvement in lipid metabolism, obesity, and osteoporosis after adrenalectomy in those patients [96].

Improvement of cardiovascular risk factors in ACS patients after adrenalectomy is controversial and the long-term benefits of adrenalectomy have not been demonstrated yet. So it is still a matter of debate that which patient will benefit from surgery.

The guidelines do not routinely recommend adrenalectomy to all patients with ACS. The AACE and American Association of Endocrine Surgeons (AAES) recommend adrenalectomy only in patients having ACS with worsening abnormal glucose tolerance, dyslipidemia, hypertension, and osteoporosis [84].

The decision of surgical treatment must be individualized for patients and presence of comorbidities, end organ damage, and age of patient, size and radiological features of tumor may dictate the approach.

21.11 Adrenal Incidentaloma

The adrenal mass larger than 1 cm detected incidentally in an imaging of patients for nonadrenal disease is called adrenal incidentaloma (AI). The lesions on imaging test of patients having cancer or hereditary adrenal disorders are outside of this definition [97]. The prevalence of AI is between 3 and 5% in imaging series [98]. The majority of AI are unilateral but bilaterally disease can be detected in approximately 15% of patients [97]. The major concern of a physician facing with adrenal incidentaloma is whether those lesions are functionally active or malignant. Although most of AI are benign and nonfunctional (up to 80%), some are hormone active (overproduction of cortisol, aldosterone, or catecholamine/metanephrine) or malignant.

A group of biochemical tests clarify the functional status of AI. Routine measurement of catecholamine, hypokalemia and hyperglycemia screening and mineralocorticoid (in case of hypertension and hypokalemia) evaluation have to be done. The evaluation of hypercortisolism is performed by 1 mg overnight DST. The threshold for diagnosing subclinical hypercortisolism remains at 1.8 μg/dL (50 nmol/L), with 95% sensitivity and 80% specificity [84].

The main issue in the chapter is the patients who need surgery for suspicion of malignancy. The procedure is mostly diagnostic and therapeutic rather than prophylactic but in borderline cases it can be accepted as prophylactic manner which will be outlined.

The computed tomographic characteristics (lipid content and washout dynamics) and size are two important criteria for malignancy assessment since the needle biopsies have limited place in the diagnosis of adrenal masses.

CT scan with non-contrast images gives information about the size and lipid content of the lesion, as well as the vascularity, contour and the homogeneity, the presence of lymph nodes and the invasion to adjacent tissues [98]. The lipid content is inversely proportional with malignancy. Hounsfield units (HU) is indicative for lipid content. A density >10 HU on the CT scan has a sensitivity of 100% and a specificity of 72% for diagnosing malignancy [99]. High contrast washout at 15 min is indicative of the benign nature of an incidentaloma on contrast CT [79, 99].

The diameter of the mass is another alerting sign for the malignancies. The adrenocortical cancer risk is 2%, 6%, and, 25% for the mass smaller than 4 cm, 4–6 cm, and larger than 6 cm, respectively [100].

Surgery usually is not recommended for AI less than 4 cm and benign imaging features. The follow-up strategies of those lesions (<4 cm, homogeneous and with low density (<10HU)) differ in guidelines of ESE and AACE/AAES. ESE does not recommend follow-up for those patients.

However, AACE/AAES suggests follow-up at 6 months, 1 year, and 2 years [86, 101].

The use of magnetic resonance imaging (MRI) rather than CT is generally indicated during childhood, adolescence, and pregnancy to avoid radiation exposure [98]. If the benign nature of the AI is not absolute on CT, additional imaging techniques like MRI [79] or 18-fluoro-2-deoxy-D-glucose positron emission tomography (18F-FDG PET) can be performed [98]. 18F-FDG PET can be used especially in the patients with cancer history.

ESE recommends that if the nonfunctional adrenal mass is indeterminate on non-contrast CT surgery without further delay, immediate additional imaging with another modality, or interval imaging in 6–12 months [79].

There is no consensus on the definition of significant growth of an adrenal tumor during follow-up. The lesion enlarging by more than 20% in volume (in addition to at least a 5 mm increase in maximum diameter) during the follow-up period, resection is recommended by ESE since malignant adrenal lesions (mostly adrenocortical carcinoma and metastases) are almost characterized by a rapid growth [102].

However, there are rare exceptions of malignant adrenal tumor with slow growth for several years [103, 104]. In those group of patients, adrenalectomy in minimally invasive manner enables exact diagnosis, prevents patient's anxiety for malignancy, waiting and defers further periodic imaging procedures with minimal morbidity in experienced centers.

The follow-up strategy by imaging methods should be individualized according to the patient history.

21.12 Conclusion

CSA is a type of preventive surgery for patients having hereditary PCC with VHL, MEN2, and NF-1 syndromes, and with small tumors on the remaining adrenal who had a previous contralateral total adrenalectomy. Several studies have reported the outcome of CSA for PCC and partial adrenalectomy for ACS but most involve cohorts with small numbers and are retrospective, uncontrolled and lack of randomization. To reach a clear-cut decision, further studies are needed.

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Omentectomy: Whether to Perform Should Be Questioned

22

Arif Atay, Yunus Sür, and Osman Nuri Dilek

22.1 Introduction

The word omentum is derived from the word "omen" (meaning sign, foreboding, or premonition) in ancient Egypt. It is one of the most described organs in warriors injured in battles and gladiator fights. Galen of Bergama (128–199 AD), a philosopher and surgeon, thought that the omentum was the part that warms the intestines [1]. Once considered as an inert adipose tissue that only provides insulation in the peritoneal cavity, today, the omentum is known to be uniquely effective in defending against pathogens and injuries and is considered a living immunological organ [2–4]. With its surface area of 300–1500 cm^2, the omentum can reach almost anywhere in the abdominal cavity [1]. Structures called "milky spot" or "omental glomeruli" rich in mesenchymal cells, mostly formed by macrophages and lymphocytes gathered around capillaries in the omentum majus, form the first-line defense system in the abdominal cavity and function as the lymphoid tissue. There is a layer (cluster) rich in macrophages on the surface of the omentum [2, 4, 5].

Fluids, antigens, particles, tumor cells, and pathogenic organisms released in the peritoneal cavity are first captured (collected) by milky spots, absorbed, and then removed from the environment through lymphatic ducts [3, 5, 6]. In inflammations that occur in the abdomen, the number of milky spots increases. Omental macrophages play a major role in initially capturing and killing tumor cells and preventing the formation of local tumor deposits [1, 7]. However, with increased tumor load, this function becomes insufficient [8]. Increased tumor volume leading to seeding or by invasion into the omental tissue surrounding the tumor contributes to tumor growth and formation of nodular forms through "the polypeptide growth hormone," which is secreted by macrophages. The "angiogenesis factor" secreted from the omentum also facilitates the attachment and growth of tumor cells [3, 5, 7]. It tries to limit contamination by wrapping around the sites of inflammatory pathologies [9]. Owing to the lymphoid aggregates contained in it, it also contributes to inflammation, tolerance, and fibrotic changes under the influence of a number of systemic impulses [3]. Moreover, the omentum is an important host defense system against bacteria [10]. In addition to the properties of adhesion formation and neovascularization, it also has a protective property against radiation damage [2].

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The omentum has a function aimed at phagocytes, collecting (gather) or controlling pathological formations by surrounding them. Because of these characteristics, Rutherford Morrison described the omentum as the "abdominal policeman" [1]. The omentum attempts to control the process by turning into a local inflammation site (Fig. 22.1). If the process progresses to infection, it tries to maintain control by allowing abscess formation. This mechanism works in plastron appendicitis, diverticulitis, and cholecystitis. This feature of the omentum contributes to the development of plastron appendicitis in cases of delayed appendicitis in diagnosis or treatment.

Considering the functional features of omentectomy in the abdominal cavity, surgeons question the necessity of performing omentectomy from time to time. For this purpose, in addition to experimental studies, clinical retrospective and prospective studies have been conducted and can be described as experimental, gastrointestinal surgery, gynecological surgery, omental pathology, and individual case studies.

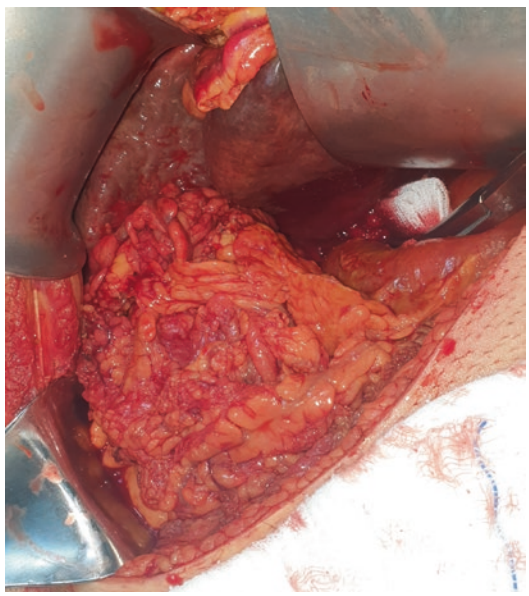

Fig. 22.1 The picture shows an effort to control the infection by surrounding the gallbladder of the omentum in a patient with acute cholecystitis

22.2 Experimental Studies

Studies have been conducted on tumor behavior in the presence or absence of the omentum. In a study by Lawrence et al. (1991) in rats subjected to colon resection and anastomosis and injected with intraluminal tumor cells, 38% and 43% of rats with intraluminal injection developed tumor in the anastomosis and omentum, but this ratio was 14% and 9% in the omentectomy group. With intraperitoneal administration, the tumor was detected as 53% in the anastomosis and 79% in the omentum, whereas in the omentectomy group, it was 16% and 29% (omental residue) [7].

In an experimental study conducted by Pinheiro et al. (2019) in Mdx mice, myoblast differentiation of HGF, FGF, and VEGF secreted by the omentum and with progenitor effect on muscles have shown that they contribute to the repair of the damage in diaphragm muscles. In mice subjected to omentectomy, the inflammatory response and NFk-B were reduced, and this recovery was disturbed [11]. As a result, it was revealed that the omentum increases inflammatory response, stimulates regeneration, and prevents fibrosis in the diaphragm muscle.

It is used to seal many defects, especially peptic ulcer perforations of the omentum. Experimental studies in rats showed that the omentum increases blood supply by adhering to the cross-section or perforation surface as it shows angiogenic activity. Increased blood supply promotes increased myofibroblasts in the wound area, accelerating the healing process [12]. In another study, it was determined that maximal acid output decreased, and ulcer healing was accelerated in gastric ulcer-generated and omentectomy-applied rats compared with the control group [13].

Studies have shown that the accumulation of fat in visceral organs leads to a disturbance of glucose and lipid metabolism and causes the development of the metabolic syndrome. In an experimental study by Garcia-Ruiz et al. (2018) on rats with obesity with a special diet, it was reported that despite the special diet in rats subjected to omentectomy, food intake decreased,

weight gain stopped, and nonalcoholic fatty liver and development of metabolic syndrome was prevented. The omentum is believed to be mediated by C-reactive protein (CRP), interleukin-6, and high lipolysis activity, leading to leptin resistance and inducing obesity. Interestingly, it was found that the weight of normal weight rats subjected to omentectomy did not change. As a result, it was noted that omentectomy might contribute to the treatment of metabolic syndrome [14]. However, clinical studies on this subject are needed.

The omentum has been claimed to have a role in collecting and spreading tumor cells, especially colon tumors. In rats with transplantable carcinogen-induced colon cancer model, Weese et al. (1988) reported that less common tumors (26%) and less small bowel obstruction (16%) occurred in rats subjected to omentectomy. In contrast, omental tumors developed more (75%) and rapidly, resulting in more (85%) small bowel obstruction in rats not subjected to omentectomy [15]. However, there are studies with conflicting results. In an experimental study conducted by Yokoyama et al. (2012) on rats to investigate the effect of omentectomy on tumor propagation and survival, it was identified that the omentum tried to capture and control tumor cells and prevent their spread, but the spread in rats subjected to omentectomy was rapid. The authors reported that the omentum with metastases could be removed, but omentectomy would be rewarding for the tumor in terms of relapse and spread [16].

To exhibit the efficacy of stem cells in the omentum, Garcia-Gomez et al. (2014) investigated the efficacy of omentectomy in rats subjected to subtotal nephrectomy. They detected a dense stem cell presence in the zone formed by adhering the omentum to the cross-sectional surface using polydextran gel particles in the group subjected to subtotal nephrectomy. Moreover, they found that plasma creatinine and urea-nitrogen levels were lower in the group without omentectomy, glomerulosclerosis and tubular damage were less developed [17].

It has also been questioned that an excessive increase in the omentum in obese patients can play a role in steatosis. It was thought that the omentum might be the source of inflammatory biomarkers (CRP, plasminogen activator inhibitor-1 activity, TNF-alpha, and fibrinogen) in the serum. However, experimental studies in rats have shown that omentectomy did not have any contribution [18].

In an experimental study to investigate whether omentectomy contributes to the formation of adhesions, it was found that the level of tissue and serum plasminogen activator decreased in rats subjected to omentectomy and the level of plasminogen activator inhibitor-1 and adhesions increased. In contrast, in rats without omentectomy, adhesions decreased. It was established that the omentum forms a mechanical barrier, and fibrinolytic substances secreted from its surface prevent adhesion [19].

22.3 Gastrointestinal Procedures

D_2/modified D_2 lymph node dissection is performed as a standard approach in patients with stomach cancer. There are numerous studies with different results regarding whether omentectomy should be performed in patients with stomach cancer. In a series of 284 patients who underwent gastrectomy, lymph node dissection, and omentectomy due to gastric tumors, Barchi et al.(2019) detected omental metastasis in only 5 patients (1.8%); omental metastasis was found more in patients with exceeded serosa and T3 lesions and ovarian and liver involvement. They reported that omentectomy should be avoided in patients with T1–T2 tumors with no metastases (M_0) less than 5.2 cm in diameter. They emphasized that tumor presence in the omentum majus lymph nodes is often encountered in terminal patients with an advanced stage of tumor invasion, recurrence, peritoneal seeding, and ovarian and liver involvement [20]. In 330 patients with advanced-stage gastric tumors, Hasegawa et al. (2013) found that 3- and 5-years survival rates were 72.9% and 66.2%, respectively, in patients who received omentectomy and 76.7% and 67.3%, respectively, in those who received the omentum-

preserving gastrectomy. As a result, they reported that there was no statistically significant difference in peritoneal involvement and survival between the omentectomy group and omentum-preserving gastrectomy group [21]. In a study based in the Netherlands, Jongerius et al. (2016) detected omental metastasis in 5% of patients in a series of 100 patients with stomach cancer; among these five patients, they detected lymph node involvement in T_3 and T_4 cases, and in three cases with T4 involvement, they found distant metastasis. In the same series, they reported that the likelihood of omental metastasis was very low in patients who are considered preoperatively resectable, with no requirement of omentectomy during radical gastrectomy [22].

In clinical trials conducted to understand the metabolic impact of omentectomy in patients with stomach cancer, it has been reported that gastric resection has impacts, especially on BMI, triglycerides, LDL, HDL, and hematological profile, but omentectomy does not have any impact on them [23]. Many clinical trials have been conducted on more significant beneficial effect of partial omentectomy [23–25]. In a series of 37 patients, Kim et al. (2011) reported no significant difference between patients who underwent partial omentectomy and total omentectomy followed for approximately 38 months. In patients undergoing radical distal gastrectomy, omentectomy is preferable owing to factors such as early-stage gastric cancer, fewer complications, and better albumin balance. However, large-scale clinical trials are needed to investigate long-term oncological outcomes [23, 24]. In a study by Kim et al. (2014) in 146 patients with mature advanced gastric cancer without exceeded serosa, statistically, in terms of duration of surgery, perioperative complications, relapse, survival, and disease-free time, no significant differences were detected. They found that the partial omentectomy group showed more advantages [25].

Studies related to *bursectomy* have also been conducted, considering it can be prognostic and offer survival advantage in patients with stomach cancer [26–28]. In a multicenter study by Kurokawa et al. (2018) including 1204 patients covering 57 hospitals in Japan, patients with gastric resection and D_2 lymph node dissection were divided into omentectomy or bursectomy groups. There was no significant difference between the groups in terms of a 5-year survival rate (76.7% and 76.9%). The authors recommended D_2 lymph node dissection and omentectomy as the standard approach in patients with stomach cancer [27]. Bursectomy is not routinely performed because it does not provide an advantage in terms of survival and results in development of additional complications; thus, it is recommended to be performed only in patients with posterior gastric wall tumors [28].

It was believed that the release of the omentum in patients who underwent colectomy for a long time would cause adhesion and obstruction in the small intestine. However, some clinical trials have found that the opposite is true. In a series including 406 patients with colectomy and ileoanal anastomosis who underwent omentectomy, Ambroze et al. (1991) found no significant difference in terms of small intestine ileus and more septic cases occurred in this group [29]. On the other hand, the opening of gastrointestinal anastomoses and fistulas remain the cause of severe morbidity and mortality. Besides, the contribution of the omentum to healing by wrapping around anastomosis has been investigated. In a study by Agnifili et al. (2004) in which anastomoses were protected with omental wrapping after 171 cases of colon resection, the positive impact of omental wraps was found in anal and colorectal surgery [30]. In coloproctological operations, the omentum should be tried to be protected, if possible.

In tumors with peritoneal involvement, complete *cytoreductive surgery* can significantly affect survival and is an aggressive operation that covers organ resection, appendectomy, liver capsulectomy, splenectomy, cholecystectomy, colectomy, mesenteric peritonectomy, and omentectomy [31]. In intra-abdominal tumors, the first organ encountered by the tumor cells in the omentum in peritoneal seeding cases where the tumor exceeds serosa and tumor load is low. In

tumors in the reach of the omentum, in the sites where the tumor lesion is tried to be surrounded, seeding cells are first captured, and the spread is tried to be prevented [6, 16]. In sites where the spread is too high, the omentum cannot bear the tumor load, and peritoneal implantations begin to form. In other words, the omentum can also be described as an organ that acts as a shield that tries to slow down the spread of the tumor. Omentectomy is one of the most common operations (93%) as the primary procedure in cytoreductive surgery that has a positive impact on survival in cases of pseudomyxoma peritonei and similar cases [32, 33].

Some studies have reported that the omentum can be preserved in patients with T_1–T_2 gastric cancer (M_0). However, in advanced cases, prospective clinical trials with more homogeneous and large groups are needed. In advanced cases, surgeons have a greater tendency to perform radical surgery and omentectomy. Discussions on the process of bursectomy are ongoing. Prospective studies are needed due to serious complications such as bleeding and fistula.

22.4 Gynecological Procedures

Omentectomy is one of the most commonly performed procedures during gynecological operations. Specifically, omentectomy plays an important role in the staging of ovarian- and endometrium-origin tumors, and omentectomy and lymph node dissection is questioned in terms of treatment planning. In 245 cases that underwent malignant ovarian germ cell tumor (MOGCTs) surgery, in terms of survival between omentectomy (96.8%) and omentectomy-preserving (100%) groups, Qin et al. (2019) reported that there was no statistical difference and that omentectomy had no prognostic value and did not provide survival advantages [34]. Similar results were obtained in a study by Xu and Li on phases 1 and 2 MOGCTs series of 223 cases, and omentectomy was not recommended in early-stage MOGCTs cases [35]. Additionally, there are authors who recommend random omental biopsy instead of total omentectomy for staging in early-stage tumors [36].

Ovarian teratoma is a well-differentiated and benign entity, commonly observed during childhood. Teratomas rarely rupture, which can lead to a reaction of granulomatous peritonitis in the omentum, and their appearance may resemble peritonitis carcinomatosis. Surgeons tend to engage in aggressive resection because the appearance on laparotomy resembles peritonitis carcinomatosis. Notably, histopathological analysis with intraoperative frozen section and more conservative treatment can be performed in these patients [37]. In a surveillance study conducted by McNally et al. (2015), it was found that omentectomy in stage 3A and below had no contribution to survival in 5454 patients who underwent omentectomy and 2404 patients with non-epithelial ovarian cancer [38]. On the other hand, omentectomy is recommended for borderline ovarian tumors observed in patients of childbearing age [39].

Omentectomy is also recommended in patients who underwent surgery due to endometrium cancer. In a series of 435 cases, Bayrak et al. (2019) reported that they detected metastases in the omentum in 5.3% of cases and micrometastases in 17.4% of these omental metastases; moreover, tumor grade I and positive peritoneal cytology and the metastasis of the omentum had a significant relationship. They also stressed that there was adjacent adnexal involvement in endometrium cancer cases and recommended performing selective omentectomy in grade 3 tumors [40].

In a meta-analysis conducted by Joo et al. (2015) in a series of 1163 patients with endometrium cancer, 83 patients (7.3%) were found to have omental metastases. Metastasis was found to be microscopic in 22 (26.5%) patients with omental metastases. The rate of microscopic omental metastasis was 1.9%, but it was found that the rate of microscopic omental metastasis was higher (8–9%) in patients with stage 1 endometrium cancer. Thus, selective omentectomy was recommended for patients with a risk of microscopic omental metastasis [41]. In another study, 37.5% of patients with grade 3 endometrioid car-

cinoma had omental involvement and the stage of the disease changed [42]. In a study by Ross et al. (2018) including 153 patients with endometrium tumor, microscopic tumors were found in 35% of patients who underwent omental sampling, and during patient surveillance, the mean survival was 11.4 months in patients with omental tumor and was 128.7 months in those without. In the same series, the mean survival was 127.7 months in patients with omental sampling and 71.3 months in those without. Omental involvement is an important prognostic factor for survival [43]. In contrast, in 106 patients with serous carcinoma in the uterus, Luz et al. (2016) detected macroscopic involvement in 6 of 66 patients who underwent omental biopsy or omentectomy, with micrometastatic involvement in 2 of them and omental involvement in 8 (12%). In their study, they found no significant difference in survival advantage between the group with omental biopsy or omentectomy (evaluation) and the group without. In addition, the authors recommended that the omentum should undergo a comprehensive intraoperative assessment [44]. Notably, there is no need for a second operation to perform omentectomy, indicating that the survival period remained unchanged following the surveillance of cases that underwent surgery due to prediagnosis of endometrium cancer but had papillary serous carcinoma that was histopathologically detected [45].

In most cases of tubal *ectopic pregnancy*, the omentum has been reported to be able to control complications due to tubal pregnancy or play a retarding role by wrapping around the tube [46]. In the literature, cases of primary omental pregnancy have also been reported [47].

Omental involvement in gynecological *tumors* occurs in 9–37.5% cases. It is acknowledged that tumor retention is important for surgical staging and planning of treatment and it is correlated with peritoneal involvement [42–44, 48]. Omental involvement is considered an indicator of poor prognosis. When performing radical surgery, it is necessary to perform omentectomy for the purpose of removing the tumor load on the omentum. However, the contribution of omentectomy to survival remains controversial. In early-stage tumors, omental involvement is minimal and omentectomy has no impact on survival, and if there is no macroscopic involvement, it is not recommended to perform omentectomy [49]. Random omental biopsies can be performed in early stages to contribute to staging.

22.5 Omental Pathologies

Omentum torsion is a very rare entity and can mimic many clinical pathologies in the abdomen. Additionally, abdominal CT is very helpful in differential diagnosis. Surgical removal of inflation/necrosis mass is sufficient in patients who do not recover by clinical follow-up and medical approach [50]. Omental torsion state can mimic appendicitis. Laparoscopy should be the first option in cases that are thought to undergo exploration for the purpose of diagnosis and treatment. In laparoscopy as well as resection of the omental necrosis site, some surgeons recommend performing appendectomy [51, 52].

Moreover, 83.3% of patients with omentum *infarction* have more than normal weight according to their average age. Recurrent ultrasound can be conducted for diagnosis. Clinically, omentum infarction can mimic appendicitis. Because conservative treatment is sufficient in most cases, appendicitis should be excluded in differential diagnosis (Fig. 22.2). In addition to partial omentectomy, incidental appendectomy may be performed in patients who underwent laparotomy/laparoscopy by consulting with the family [53].

The omentum also plays a role in limiting and controlling infections that settle in the abdomen. Depending on the damage caused by the infection to the omentum, it may be necessary to perform omentectomy. There are cases in the literature with laparotomy for abscesses caused by melioidosis (*Burkholderia pseudomallei)* [54]. Omentectomy may be performed depending on mass image in patients with pelvic actinomycosis and the appearance of tumor implant in omental involvement [55]. Omental involvement is also common in patients with abdominal tuberculosis and can imitate an ovarian tumor. To avoid unnecessary radical surgical

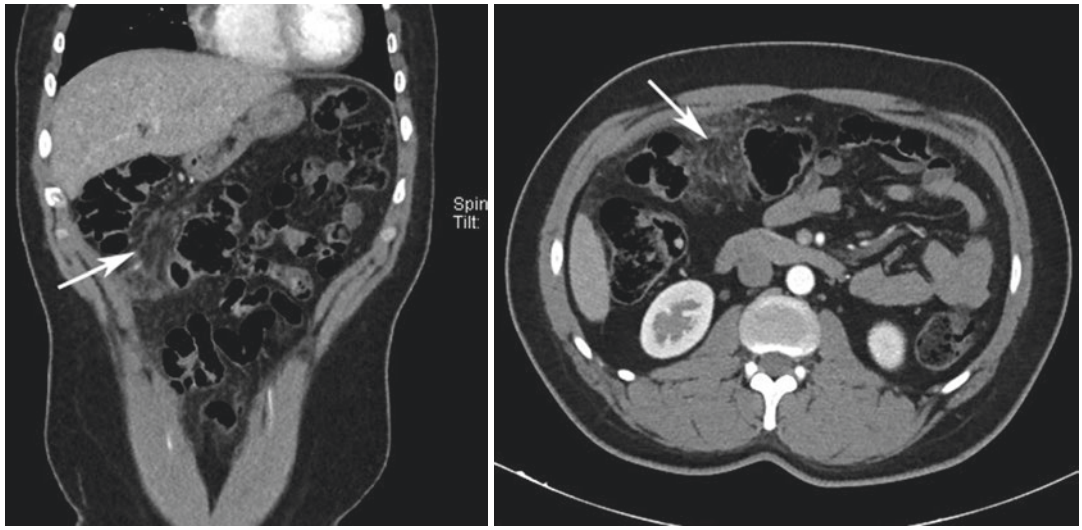

Fig. 22.2 CT image of a patient with omental necrosis (Arrow) detected in the postoperative period

resection, laparoscopic expressions and biopsy are diagnostic. In diagnosed cases, medical treatment is recommended [56].

The omentum captures, limits, and tries to maintain the contents or materials remaining in the abdominal cavity after surgeries. Before conducting a radical surgical intervention due to the omental mass, a good anamnesis should be obtained and the source of the omental mass should be investigated. In many cases wherein the cause can be determined, follow-up should be sufficient. Spilled and not removed stones from the gallbladder, perforated during laparoscopic cholecystectomies, are wrapped by the omentum and can turn into an inflammatory mass [57]. Stones that do not exhibit clinical symptoms can be traced. However, due to rarely *spilled stones*, internal or external fistulas can also develop from abscesses surrounded by the omentum. In such cases, abscess drainage, irritation, and removal of traction without removing the omentum may be sufficient.

22.6 Miscellaneous Conditions

The functions of the omentum to find, capture, and surround foreign bodies can lead to undesirable situations in the clinic. Primarily, the omentum faces complications related to hematoma, ischemic area, incision lines, suture materials, and defects formed in the abdominal cavity after surgeries. The contribution of the omentum to the inflammatory process here can occasionally result in the formation of brides. In the literature, some studies reported that the omentum prevents the formation of brides in contrast to what is generally believed. The omentum aims to prevent adhesions with fibrinolytic factors secreted from its surface [19].

In a study by Araike et al. (2015) including 113 patients operated due to intestine obstruction due to brides, as a result of a 5-year follow-up, the bride ileus recurred in 18 patients (20.8%). In multivariate analysis, it was found that 87.9% of patients underwent omentectomy and 53.8% of those who did not undergo omentectomy had brides. It was found that 54.5% of patients who developed bride ileus underwent omentectomy and 21.3% did not undergo omentectomy. Omentectomy is an independent risk factor for bride formation and bride ileus development [58].

Excessively increasing omental and visceral adipose tissue in obese patients is a factor that adversely affects morbidity and mortality. In a meta-analysis study conducted by Lee et al. (2018), the addition of omentectomy to bariatric surgery had no positive impact other than resulting in statistically significant reduction in BMI,

although minimal. There was no significant difference in both groups in terms of metabolism and cytokines. Only in patients who underwent bariatric procedures, HDL lipoprotein was significantly increased [18]. In a similar study by Andersson et al. (2014), adding omentectomy to Roux en-Y gastric bypass did not have a positive impact on reducing insulin resistance and cardiometabolic risks [59]. Although there are metabolically positive feedbacks in similar cases wherein omentectomy is added to Roux-en-Y gastric bypass in the literature, extensive and prospective studies are needed [60]. In the study by Tamboli et al. (2011), after Roux-en-Y gastric bypass surgery, there was a decrease in the release of inflammatory genes and inflammation in the skeletal muscles and this was observed more in patients undergoing omentectomy [61]. In patients with metabolic syndrome who underwent partial jejunum resection in addition to omentectomy, especially intestinal system surgical procedures to control type 2 DM, better results have been obtained in terms of metabolism profile [62].

Peritoneal dialysis *catheter obstruction* is a common problem in the clinic (23–36%). Malposition and development of omental wrap are the most commonly reported causes. In the literature, it was noted that some of the patients with catheter dysfunction underwent partial omentectomy and the catheters were made functional [63–65]. On the other hand, in a series of 154 pediatric patients with peritoneal dialysis catheter, it was found that omentectomy did not contribute to catheter obstruction, mainly due to technical problems [65]. Currently, catheter types are more prominent in terms of dysfunction. Moreover, some authors recommend laparoscopic placement of the catheter, partial omentectomy, and omentoplasty [66].

Idiopathic omental hemorrhage is very rare, but it can lead to life-threatening hemorrhages. Trauma, aneurysm, and vasculitis are the main causes of omental hemorrhage, and signs of hypovolemia can be dominating. In the differential diagnosis of the disease that mimics the acute abdomen, abdominal CT may be useful. In addition, with angiography, information about the location of bleeding and whether it is caused by tumors can be obtained or laparotomy or laparoscopy may not be required due to embolization. In laparotomy cases, hemostasis and partial omentum resection can be performed [67].

In inguinal hernia *incarceration*, the contents of the hernia are important in the approach to monitor and for follow-up. Filling the hernia defect by the omentum will reduce the risk of strangulation of bowel loops (Fig. 22.3). In a study by Houben et al. (2015) including 2184

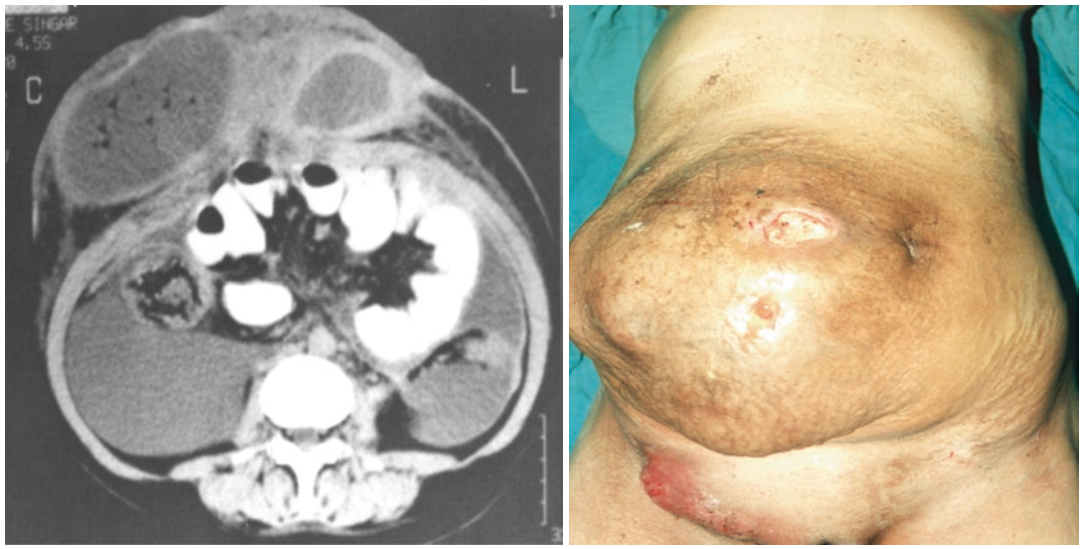

Fig. 22.3 CT view of omental strangulation and necrosis findings in our patient who underwent laparotomy due to strangulated incisional hernia and right femoral hernia

patients with pediatric hernia, irreducible (incarcerated) hernia was detected in 1.6% patients, whereas hernia was frequently detected in the intestines in males (62%) and in the hernia sac and ovary in females (62%); it was determined that the omentum formed the contents of the incarcerated hernia at a frequency of 12%. In half of these cases, partial omentectomy was performed [68].

In an obese patient who was followed by ventilator support due to multiple fractures of bones, abdominal lipectomy and omentectomy performed to lower intra-abdominal pressure and prevent lung complications. On postoperative day 1, the tidal volume significantly increased, and the patient was removed from mechanical ventilator support on postoperative day 14 [69].

22.6.1 Omentectomy/Omentoplasty

The omentum majus can be partially and totally removed. In the clinic, infracolic omentectomy is preferred due to gynecological tumors and total omentectomy (major and lower) is performed in stomach cancer and patients who underwent HIPEC procedure. When performing lesser omentectomy and bursectomy, dissection of the part with the extension of the ligamentum venosum should be performed after binding. Otherwise, bleeding may occur from the cranial side due to its connection with the left hepatic vein [70]. Omentectomy can be performed with open, laparoscopic, or robotic surgery.

Omental flaps are often used in gastrointestinal tract surgery and are mainly used as patches for peptic ulcer perforations (Graham technique), as omental wrap in colon anastomoses, and as a filling material for liver hydatid cysts. Omental transposition scan protect it from pelvic radiation and radiation enteritis, especially by covering the small intestines and ensuring by enveloping them. The omentum is also used in a large number of procedures related to plastic surgery. Omental grafts (flaps) can also be used for procedures such as revascularization of ischemic legs, enclosing, reconstruction, fistula revision, fillers, or protective shielding [71, 72].

22.7 Conclusion

The omentum is one of the first organs affected by inflammatory and pathological events in the abdomen. It is a unique organ with its mobility and physiological tasks. Its main characteristic is closely monitoring and controlling the pathological processes developing in the abdomen. Moreover, the omentum is considered the "*abdominal policeman.*" With the function of limiting and controlling inflammatory and infectious pathologies, it somewhat provides the patient's survival. While trying to perform the same function in tumors as well, the stage of the disease changes as a result of its inability to cope with the increased tumor load, and thus, it is considered an indicator of poor prognosis. Due to this feature, it is one of the first sacrificed organs in radical surgeries. However, whether resection of the omentum is necessary should be questioned according to each pathological process.

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23 Open Access in Laparoscopic Surgery to Prevent Entry Complications

Viktor Justin, Diletta Di Miceli, and Selman Uranues

23.1 Introduction

To reduce complication rates in surgery, refining of techniques is a mainstay and starts as early as preoperative preparation and pre-habilitation of the patient. Concerning laparoscopic surgery, the first complication may arise when access to the abdominal cavity is performed and pneumoperitoneum is established. While adverse events must be reduced by any means in all kinds of surgery, this especially holds true in preventive surgery. Imagining the sequelae that could arise from a laparoscopic access injury, e.g., to a major vessel such as the pelvic vessels in a case of elective or opportunistic appendectomy, must be one of the worst nightmares for every surgeon.

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More than 50% of accidental bowel and (major) vascular injuries in laparoscopy are associated with entry techniques. Major entry-related complications occur in up to 0.6% of patients, with about 70% related to the first trocar placement [1–6].

The intestines with up to 37.6% of all injuries are the most affected organs, followed by vascular injuries to major vessels such as the iliac vein/artery, aorta, and visceral vessels [2]. Depending on the degree of injury and time of recognition, substantial morbidity and mortality can arise [7, 8]. Apart from surgeon skill and experience, risk factors for visceral injury include pre-existing adhesion due to operations or infection. While only scarcely present in not operated individuals, umbilical adhesions have been described in up to 15% of women with previous laparoscopies and rise up to 60% after previous median laparotomy [9–12]. In vascular injuries, an underestimation of the proximity of vascular structures, forceful thrust, and inadequate pneumoperitoneum (among other factors) may be fatal [13]. In other than obese individuals, the distance between the umbilicus and the retroperitoneal vasculature may only measure 2 cm and thus is easily reached with either trocar or Veress needle [14, 15].

To address this problem, multiple techniques have been described over time and can be divided into closed and open access techniques. Closed access can be achieved with or without previous establishment of pneumoperitoneum after puncture with a Veress needle. While the umbilicus is

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the usual site for Veress needle insufflation, the so-called *Palmers* point in the left upper quadrant can be used in case of expected umbilical adhesions [16]. Alternatively, transvaginal or intercostal approaches have been described [5].

Trocars for closed access can be bladeless or cutting (with or without shielded blades), blunt or conically tipped. Optical trocars can provide certain visualization while penetrating the abdominal wall. While several open access techniques exist, the most known, which requires a special trocar, has been published by Hasson [17].

Especially in previously operated patients, blind puncture of the abdomen (either by Veress needle or gasless introduction of the first trocar) carries a higher risk of serious entry injuries, especially when adhesion of bowel loops cannot be safely ruled out.

A recently updated Cochrane review [18] compared 25 entry techniques including results from 57 RCTs with a total of 9865 patients. The authors found no evidence of differences in major complications and generally described the quality of evidence as low or very low with too small sample sizes to identify differences. Only a reduced rate of failed entry was observed in open access techniques. Of note, the majority of studies selected low risk, non-obese patients without previous abdominal surgery and thus may not reflect real-life clinical data. Consequently, there is no consensus favoring one access technique over another, and the methods used vary with surgeons' preferences being affected by training, experience, and regional and interdisciplinary considerations [19].

23.2 A Safe Technique

We advocate a simple, reproducible technique for open access that can be employed in all types of patients. While this technique can be used at any site of the abdomen, it is preferably done at the upper edge of the umbilicus, because here the subcutaneous fat is at its thinnest and the fascia is easily reached, even in obese patients [14].

Operative steps:

1. An approximately 1.5 cm vertical incision is performed from the bottom to the upper edge of the umbilicus (Fig. 23.1).
2. The subcutaneous fatty tissue is dissected, and the fascia exposed.
3. The fascia is then grasped vertically on both sides with Kocher clamps creating a fascial fold (Fig. 23.2). This way the risk of accidental injury to the peritoneum and intra-abdominal organs can be avoided.
4. The fascia is then carefully incised, thus opening the preperitoneal space (Fig. 23.3).
5. When the preperitoneal space is reached, the Kocher clamps will be turned 90° and will grasp the fascial edges: this way the fascia unfolds, and the incision is lengthened (Fig. 23.4).

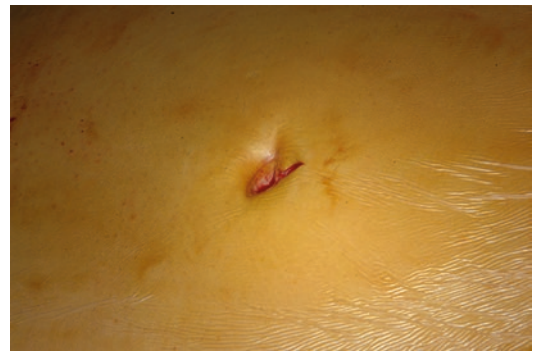

Fig. 23.1 Umbilical skin incision

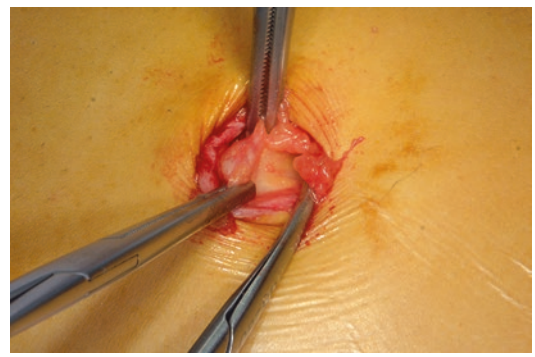

Fig. 23.2 Grasping the fascia with Kocher clamps

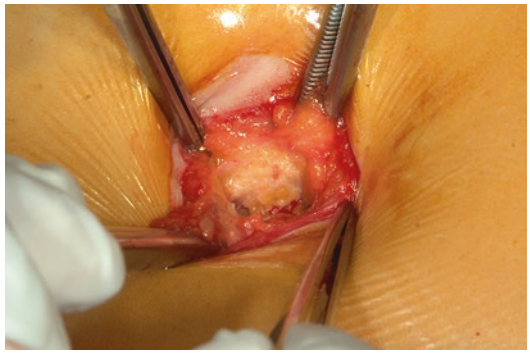

Fig. 23.3 Fascial incision

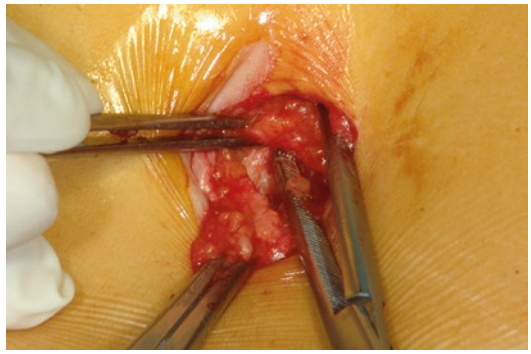

Fig. 23.4 90° rotation and thus change of the grasper from longitudinal position to transverse position

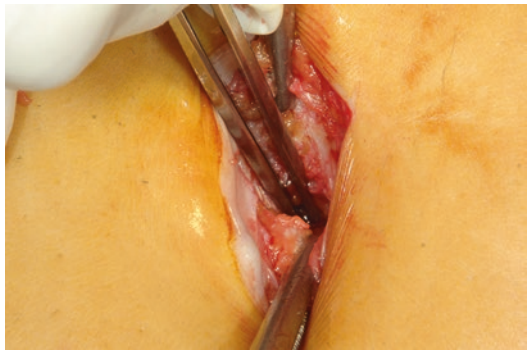

Fig. 23.5 Peritoneal incision with peritoneal access

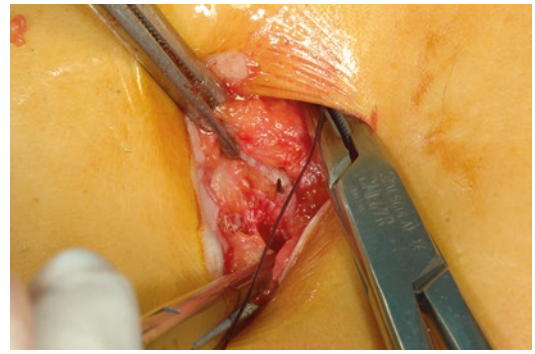

Fig. 23.6 Placement of fascial suture

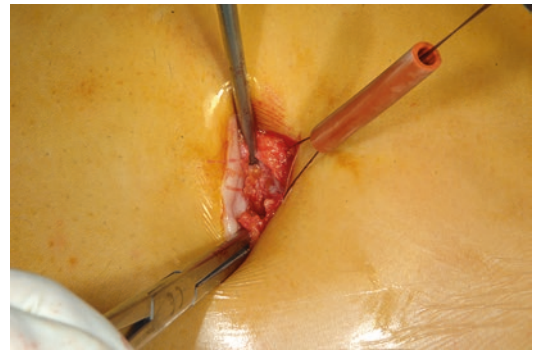

Fig. 23.7 Placement of a tourniquet

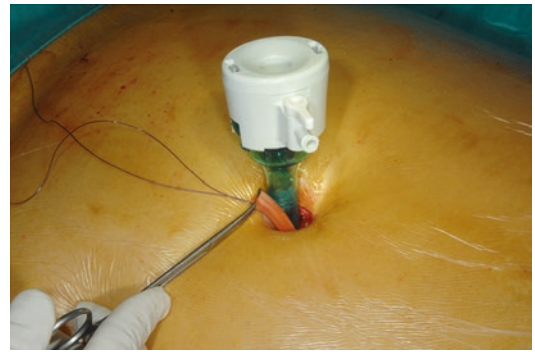

Fig. 23.8 The fascia is tightened around the trocar to prevent gas leakage

6. The parietal peritoneum now is carefully grasped and incised (Fig. 23.5). The incision can be digitally enlarged and the intra-abdominal area around the incision can be palpated for potential adhesions. Now the peritoneal cavity can be seen through the incision.

7. Before the first trocar is introduced, a fascial suture (#0 or #2-0 usually slowly absorbable such as Biosyn™) is placed (Fig. 23.6). It is then fed through a tourniquet that is tightened at the entry site, thus avoiding gas loss (Figs. 23.7 and 23.8). This way there is no need for a specially designed, eventually

expensive trocar, and full mobility of the trocar as well as minimal gas loss is procured. Furthermore, any necessary material (mesh, etc.) can be easily introduced and specimens quickly retrieved by opening of the tourniquet. At the end of the surgery, the previously laid sutures speed up fascial closure.

8. After establishment of pneumoperitoneum and introduction of the optic, the abdominal cavity, beginning with the area below the entry site, is evaluated for any potential access-related injuries.

This technique has been published previously [19] with a 0.09% complication rate (2/2258 patients) as compared to 0.9% (3/321) at a single institution. Both complications were handled via the established access without need for conversion. The mean time needed for establishment of pneumoperitoneum did not differ whether by open access or Veress needle. With this technique, possible complications associated with blind puncture may be prevented without additional time consumption or cost. Access-related complications may be detected early at the time of the peritoneal access and directly managed. Disadvantages of open trocar placement, such as carbon dioxide leakage, are prevented by the tourniquet. Specimen retrieval is facilitated, and fascial closure is accelerated.

Ultimately, irrespective of the method used for first trocar placement, all following trocars should be placed under direct visualization.

23.3 Conclusions

While selection of access modality depends on the surgeon's preference and experience, open access techniques are advisable in order to prevent access complications. The presented technique is safe, reproducible, and easy to apply without additional cost or time consumption.

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Prophylactic Surgery in Trauma

24

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24.1 Introduction

The concept of prophylactic surgery, or surgery in trauma is designed to prevent complications for the most part, and the literature is not abundant, when compared to other fields in surgery [1, 2].

In the setting of trauma, the field has evolved particularly with the incorporation of surgical critical care and emergency general surgery to form a broader field of acute care surgery. This reverse transformation of trauma surgery goes back to the routes of true general surgery, when most surgeons were true general surgeons. Given that trauma is not purely a disease process of operative decision making, the field of trauma has evolved to span the gamut of trauma as a chronologic disease—namely, prevention, treatment, and rehabilitation. Most trauma systems have implemented robust injury prevention and outreach programs designed to work with their local communities on efforts to mitigate the risk of traumatic injuries through education and training (e.g., motor vehicle safety, falls prevention, helmet awareness for bicycles, and violence counseling) [3]. This form of prophylaxis is invaluable in preventing trauma as a surgical disease, managed by surgeons in multidisciplinary approach.

The chapter is organized into the following anatomic categories: head, cervical spine and spinal cord, neck, chest, abdomen/pelvis, perineum/rectum, and extremities. In each anatomic category, specific examples of procedures are discussed with respect to indications and effects on disease prevention/mitigation with supporting literature.

24.2 Head

The guiding principles behind the overall management of traumatic brain injury are centered around mitigation/prophylaxis, in addition to cure when injuries do happen. In contrast to intracranial lesions that benefit from resection, intracranial traumatic injury in order to be curative needs to happen in a timely manner. Such examples are decompressing craniotomy for major subdural hematoma or epidural hematoma that can be lifesaving. The initial resuscitation and surgical decompression/evacuation, and the ensuing medical management are designed to prevent secondary brain injury. The use of intracranial pressure (ICP) monitors is itself a prophylactic monitoring, aimed at mitigating the risks of further damage. The hallmarks of secondary brain injury are hypotension and hypoxia. For

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this reason, patients deemed to have severe traumatic brain injury (defined as Glasgow Coma Score of ≤8) are recommended to have prompt initiation of mechanical ventilation [3].

Liberation from mechanical ventilation in this subset of patients is a process that can range from days to months. Early tracheostomy (defined as within 7–8 days of endotracheal intubation) is associated with a shorter intensive care unit and hospital lengths of stay, and shorter duration of mechanical ventilation [4]. Although the correlation between early tracheostomy and improved long-term neurologic recovery has been reported [5], still it is unclear whether early tracheostomy confers any benefit upon infectious complications or mortality. Nonetheless, early tracheostomy in severe traumatic brain injury patients is a Level IIA recommendation for early tracheostomy by the Brain Trauma Foundation [3]. In our practice, we attempt to perform a tracheostomy in these patients as early as possible.

24.3 Spine and Spinal Cord

Similar to traumatic brain injury, the neurologic deficits incurred after traumatic spinal cord injury are related to both primary injury (compression, shear, contusion) and secondary injury (ischemia, inflammation) [6, 7]. While surgical decompression and stabilization is commonly performed in the setting of traumatic spinal cord injury or even in complete cord transaction, its timing and the surgical intervention is not clear. Furthermore, treatment of acute central cord syndrome in the absence of associated fractures is controversial. There are no benefit to immediate surgical intervention with respect to neurologic outcomes, and some advocate non-operative management [8, 9]. More recent retrospective studies and meta-analyses have demonstrated a benefit of surgery [10, 11]. Early decompressive surgery in spinal cord injury has demonstrated both short- and long-term benefits with respect to neurologic recovery [12].

24.4 Neck Injuries

Cervical spinal cord injury is associated with a wide range of clinical presentations depending on the level of injury. Those with spinal cord injuries above the level of the fourth cervical vertebra have severe respiratory insufficiency and a significant proportion of these patients require mechanical ventilation for prolonged durations [13, 14]. The factors predictive of requiring tracheostomy amongst this population have been reported [15, 16]. As with traumatic brain injury patients, the timing of tracheostomy and potential benefits of early tracheostomy remain unclear, although early tracheostomy with respect to resource utilization (length of stay, duration of mechanical ventilation) has been reported [17, 18]. Two studies using national trauma databases have demonstrated that early tracheostomy in patients with cervical spinal cord injury is associated with lower rates of respiratory complications, shorter duration of mechanical ventilation, and lower hospital and intensive care unit lengths of stay [19, 20]. Tracheostomy as a procedure for this subset of patients is a measure of prophylaxis against post-injury complications and morbidity [21–24].

Other benefits of early tracheostomy are reduction of requirement for deeper sedation, shorter duration of mechanical ventilation, earlier mobilization, and improved resource utilization, albeit with no effect on mortality [25, 26] although this is controversial [27, 28]. Ultimately, proper patient selection is important [29].

24.5 Chest

24.5.1 Pneumothorax

Penetrating and blunt mechanisms of trauma to the thoracic cavity are common, with a reported frequency of up to 10% amongst patients admitted to hospitals after injury [30]. The diagnosis of pneumothorax is common in trauma patients. Most often, pneumothorax is associated with violation of the pleura or lung parenchyma in the setting of penetrating or blunt trauma, whereas pneumothorax can constitute life-threatening emergency if untreated in a timely fashion. The new CT scan has become a modality to diagnose the "occult" pneumothorax [31–33]. The issue that is controversial is when to drain the pneumothorax in patients that undergo major surgery and mechanical ventilation [34–37]. In our practice,

patients with occult pneumothorax are watched carefully during surgery, and clear "handover" between the trauma team and anesthesia team is mandatory. For any major surgery, the entire chest should be prepped and draped, and if at any point the patient is not doing well during the surgery such as dropping oxygen saturation or having difficulties ventilating, a tube thoracostomy should be placed at once.

24.5.2 Hemothorax

Another important sequela of chest trauma is bleeding into the pleural cavity or hemothorax. Whether the bleeding is massive or not, the initial step in management involves tube thoracostomy to decompress the pleura with evacuation of the hemothorax [38]. The majority of patients with hemothorax can successfully be treated with tube thoracostomy followed by restoration of volume, analgesics [39, 40]. However, a subset of patients with traumatic hemothorax, if not drained in a timely fashion, will progress to having retained pleural collections despite tube thoracostomy. In these patients, surgical evacuation of the hemothorax typically in the form of video-assisted thoracoscopic surgery (VATS) is required [41]. The surgical evacuation of retained hemothorax is accepted as a mainstay of care, but the timing of VATS only in recent years has become standard of care [42, 43].

24.5.3 Pulmonary Embolus

Venous thromboembolism (VTE) includes both deep vein thrombosis (DVT) and pulmonary embolus (PE), and is a potentially life-threatening complication in trauma patients and may have significant morbidity and mortality [44]. The incidence of VTE has been reported in 2–50% of trauma patients [45–47]. The PE, as the most serious complication of VTE, may require pulmonary embolectomy, but consist of therapeutic anticoagulation. Certain subpopulations of trauma (those with traumatic brain injury or spinal cord injury and those with active bleeding) have contraindications to either pharmacologic VTE prophylaxis or pharmacologic therapy of diagnosed DVT. In such patients, inferior vena cava (IVC) filters have been used since the 1970s as prophylaxis against clot propagation and development of a fatal PE [48, 49].

Though the insertion of IVC filters is pretty safe, there are still periprocedural risks [50]. Moreover, modern IVC filters are designed to be retrievable after resolution of the acute phase of disease [51]. The indications for IVC filter placement continues to be a matter of debate [52].

24.6 Abdomen and Pelvis

The paradigm shift from operative to non-operative management in blunt solid organ injury has become the standard of care in the hemodynamically stable patient. Many low-grade hepatic and splenic injuries can be managed non-operatively [53]. While it is generally accepted that angioembolization should be performed in patients who have the presence of a contrast blush on computed tomography or exhibit clinical evidence of ongoing bleeding, the role of prophylactic embolization to prevent complications remains controversial [54, 55].

24.6.1 Prophylactic Splenectomy or Splenic Embolization in Patients with Severe Traumatic Brain Injury

In patients with severe traumatic brain injury (TBI), it is important to prevent hypotension, hypoxia, and cerebral hypoperfusion [56, 57]. Data regarding angioembolization in patients with both TBI and splenic injury have failed to show any significant mortality benefit of splenectomy [58, 59]. However, older age, higher grade splenic injury, and larger quantities of hemoperitoneum have been implicated with higher rates of failure of non-operative management. As such, it is imperative to have close hemodynamic monitoring and the ability to rapidly transfuse blood products in order to prevent hypotension [60]. In patients with severe head injuries combined with high risk of failure of

non-operative management, prophylactic splenectomy for even low-grade splenic injuries must be considered. Furthermore, there should be a low threshold to proceed with splenic or liver angioembolization in these patients in order to prevent a secondary insult to the brain following TBI. Additional considerations should be made in the case of patients being transferred from hospitals not equipped with capabilities to manage complex trauma patients. Patients who will have prolonged transport times may benefit from pre-transfer splenic angioembolization if there is concern for hypotension in the setting of a severe traumatic brain injury.

24.6.2 Repeat Imaging and Angioembolization of Hepatic and Splenic Pseudoaneurysms

Hepatic and splenic artery pseudoaneurysm formation is a known complication of both blunt and penetrating hepatic and splenic trauma that can potentially lead to a life-threatening delayed hemorrhage. While the suspicion of a post-traumatic pseudoaneurysm can be suggested by symptoms such as abdominal pain, hematemesis, and melena, the true incidence of pseudoaneurysm development is unknown as many patients without symptomatology have no indications for repeat radiographic imaging [61]. Patients with asymptomatic pseudoaneurysm should undergo prophylactic angioembolization as a subset of those patients will go on to develop rupture of a pseudoaneurysm [62]. Post-hospital management in patients with blunt solid organ injury, and when to return to full activity or contact sports is widely debated. As the incidence of post-traumatic pseudoaneurysm increases with severity of splenic injury, a follow-up imaging in patients with higher grade injuries to rule out pseudoaneurysm formation should be performed [62]. Activity restrictions have been generally based on grade of solid organ injury as well as clinical judgement, with low-grade injuries having activity limitations between 4 and 8 weeks and higher grade injury limitations for 8–12 weeks [62, 63]. Athletes with a high-grade splenic injury, participating in contact sports may benefit from prophylactic splenic angioembolization to minimize the risk of delayed hemorrhage from pseudoaneurysm rupture, although the data is missing. Other high-risk populations such as those with frequent falls, or those on anticoagulant and antiplatelet medications should also be considered for prophylactic embolization if there is a higher grade injury or if the patient has comorbidities that increases their risk of subsequent pseudoaneurysm formation.

24.7 Genitourinary System

24.7.1 Prophylactic Ureteral Stent Placement for Management of Renal Trauma And Ureteral Injury Prevention

In an effort to minimize the risks of iatrogenic trauma caused during surgical intervention, the use of prophylactic ureteral stents has emerged as a beneficial tool in pelvic surgery during urologic, colorectal, and gynecologic procedures [64, 65]. Proponents of prophylactic ureteral catheterization cite the enhanced ability to diagnose potential injuries intraoperatively, facilitating early repair and avoidance of additional procedures and interventions [66]. Yet, there have been mixed results regarding whether or not there is an overall reduction in ureteral injury [66, 67]. Pre-operative stenting to prevent injury to the ureters during trauma laparotomy is not a practice, mostly due to emergency of these cases, unless there is expecting injury to the kidney. In the setting of renal trauma, particularly the renal pelvis, associated with concern for urinoma formation, prophylactic ureteral stent placement remains the standard of care to divert urinary flow away from the injury and into the normal route of excretion.

24.7.2 Prophylactic Suprapubic Catheterization for Urethral Trauma

Urinary diversion via suprapubic catheter may be preferable in cases of perineal and urethral trauma. Urethral injury is often a consequence of blunt trauma and is frequently associated with pelvic fractures—the reported incidence of male and female urethral injuries associated with pelvic trauma ranges between 4–19% and 6%, respectively. Early prophylactic urinary diversion which is often performed in conjunction with fecal diversion for complex perineal wounds can minimize wound contamination and promote early healing [87]. Suprapubic catheter placement may also be utilized in a prophylactic manner in the long-term urinary tract management of spinal cord injury patients as well. Similar to prophylactic early tracheostomy following spinal cord injury as a means to reduce the complications associated with prolonged mechanical ventilation, prophylactic suprapubic catheter placement aims to reduce the detrimental effects of chronic urinary tract infections caused by intermittent catheterizations and incomplete bladder emptying [68]. Suprapubic catheter placement can be placed percutaneously at bedside using either sonographic or cystoscopic guidance, thus avoiding the morbidity associated with operative urinary diversion [69], or during the laparotomy for trauma.

24.8 Anorectal and Perineal Injuries (Pelvis)

24.8.1 Fecal Diversion for Rectal Injury

Management of rectal injuries had previously been dictated by experiences and data collected during wartime, with the "four Ds"—debridement, diversion, drainage, and distal washout—being the mainstay of treatment [70, 71]. In non-combat hospitals, rectal injuries are primarily due to penetrating trauma, followed by blunt traumatic injuries and foreign body injuries, respectively. Of the penetrating trauma, 85–90% of cases are related to gunshot wounds, whereas stab wounds comprise approximately 5% of cases [72, 73]. More recent literature has questioned the adage of the "four Ds" as studies have shown that mandatory diversion is not always necessary [74, 75]. The decision to perform a prophylactic diversion, however, should take into account patient factors including their overall hemodynamic stability, concomitant injuries, and intra-abdominal contamination, as well as timing from injury.

Described by the Rectum Injury Scale, rectal trauma can be divided into intraperitoneal and extraperitoneal injuries, and the extent of injury can be classified as either a non-destructive injury, in which the defect is less 50% of the rectal circumference; or destructive, in which the defect is greater than 50% [75]. Intraperitoneal rectal injuries should be managed in a similar fashion to colonic trauma in the sense that the severity of the rectal injury should determine the necessity of diversion. It has been well documented in the literature that non-destructive injuries to the intraperitoneal rectum can be repaired primarily, while destructive injuries should undergo resection of the injured, devitalized tissue and primary anastomosis. A 2001 prospective multi-institutional study by Demetriades et al. found that primary anastomosis after resection for colonic injury did not increase the colon-related abdominal complications or patient mortality [76]. Extraperitoneal rectal injuries, however, provide a unique challenge as their anatomic location deep within the pelvis makes surgical repair or anastomosis difficult. A limited number of small cohort studies and case reports describe successful conservative management of these injuries without fecal diversion, citing similar mortality rates to those patients for which a diverting ostomy was performed [77, 78]. Despite an overall paucity of data, an analysis of 14 studies revealed higher infectious complications in the non-diverted group, leading to a conditional recommendation of colonic diversion in patients with both non-destructive and destructive extraperitoneal rectal injury [79].

Regardless of intraperitoneal or extraperitoneal location, other factors that should prompt the surgeon to consider a prophylactic fecal diversion include: concern with vascular perfusion to the rectum, ongoing systemic shock, concomitant pancreatic and genitourinary injuries, or known immunosuppression [80]. High transfusion requirements (over 6 units of packed red blood cells) and medical comorbidities have also been shown to increase patient morbidity and rectal related abdominal complications, and should be taken into consideration during operative decision making [81].

Diversion can be in the form of a loop ileostomy or colostomy, and while patient factors should guide which operation to proceed with, both open and laparoscopic approaches have been reported [82, 83]. The decision to perform diversion in the form of an ileostomy or colostomy is primarily up to surgeon preference, as there are few studies comparing the two specifically with regard to rectal trauma. Proponents of loop ileostomy cite the lower rates of stomal prolapse and lower rates of wound infection following stoma closure compared to colostomy [84]. Those against fecal diversion argue the need to consider the potential complications associated with ostomy takedown in addition to the quality of life factors of caring for an ostomy [85]. In patients who are diverted, the timing of ostomy reversal—especially in destructive extraperitoneal rectal injuries—should be dictated by the time it takes for the injury to completely heal. Imaging in the form of a contrast enema, as well as findings on digital rectal exam and proctoscopy can be used as adjuncts in the decision-making process [84].

24.8.2 Fecal Diversion for Perineal Trauma

Severe anorectal trauma from both blunt and penetrating mechanisms often has associated soft tissue injury. Complex lacerations and soft tissue avulsion can be exceeding difficulty to manage in the perineal region as contamination from the ano-genital tracts inevitably occurs even with meticulous attention to patient hygiene. Additionally, trauma patients may need to remain in a supine position for management of their associated injuries which can place unwanted pressure on already compromised tissue, further hindering wound healing. Fecal management systems in which an intra-rectal catheter is placed to divert stool away from perineal skin and wounds can be used as a temporary measure; however, prolonged use can lead to mucosal necrosis, anorectal fistulas, and anal sphincter atony [86]. A prophylactic diverting ostomy can assist in wound management by limiting fecal contamination, thus decreasing the morbidity associated with wound infections, dehiscence, and delayed healing [87]. Anorectal avulsions or injury to the anal sphincter leading to fecal incontinence should also prompt consideration of fecal diversion.

Ultimately, fecal diversion is not truly therapeutic per se as the diversion itself does not repair the rectal or soft tissue injuries, but it is rather a form of prophylaxis to prevent fecal contamination of the extraperitoneal and soft tissue spaces, thereby preventing sepsis and delayed healing.

24.9 Extremity Injuries

24.9.1 Limb Salvage and Compartment Syndrome: The Role of Prophylactic Fasciotomy

Trauma to both upper and lower extremities can result in fractures, neurovascular injury, and damage to muscles and soft tissues. Management of such injuries is predicated upon limb salvage strategies aimed at maintaining or restoring blood flow, repairing alignment of the skeletal structures, and preserving soft tissue coverage. In addition, it is important to note that the extremities are comprised of non-expansile tissue compartments that are at risk for elevated pressures within, giving rise to potentially serious consequences for both limb and life [88, 89]. Though the measurement of pressures within extremity compartments can be measured directly using a

variety of pressure gauges, the diagnosis of compartment syndrome has classically been a clinical diagnosis based on agreed upon criteria such as pain, absence of pulse, pallor, paresthesia, and paralysis [90, 91]. While it is clear that a diagnosis of compartment syndrome must give rise to prompt decompression in the form of fasciotomy, it can often be challenging in the setting of trauma to predict the pattern of injury that can lead to compartment syndrome [92, 93]. Several risk factors for the development of compartment syndrome have been identified in the literature, including hypotension, massive soft tissue injury, and prolonged vascular compromise (whether due to vascular injury, or tourniquet application for hemostasis) [94–96].

Once a diagnosis of compartment syndrome is made, a delay in decompression leads to significant morbidity and eventually, mortality [97, 98]. Prophylactic fasciotomy to prevent compartment syndrome prior to its occurrence in patients with severe traumatic extremity injury, based on known or hypothesized predisposition towards the development of the disease is controversial. Proponents of early, or prophylactic, fasciotomy cite the benefits of avoiding the dreaded and significant consequences of compartment syndrome upon both limb and life, amongst high risk [96, 99, 100]. However, several investigators argue that prophylactic fasciotomy is ill-advised. Such studies point to increased rates of nerve injury, higher infection rates, delayed closure of fasciotomies giving rise to increased length of stay and need for re-operation, and a general maxim that fasciotomies are performed too often and unnecessarily [101–103]. Farber et al. using a large national trauma database, demonstrated that patients undergoing early fasciotomy after vascular repair in the setting of trauma had lower rates of infection and amputation, and shorter hospital length of stay [104].

It is clear that prophylactic fasciotomy is associated with both merit and risk for the prevention of extremity compartment syndrome in the setting of trauma; however, as with all interventions, early or prophylactic fasciotomy is not without risk, and maximizing its potential benefits is contingent upon proper patient selection.

24.9.2 Prioritizing Life over Limb: The Role of Prophylactic Early Amputation

Traumatic injuries to extremities are typically managed in a multidisciplinary fashion with the guiding principles of fracture reduction/operative fixation, restoration of blood flow, and soft tissue debridement/coverage with the overriding goal of limb salvage. Though these principles form the cornerstones of treatment for extremity injuries, the preservation of life over limb dictates that limb salvage must not place the patient at significant risk of harm from life-threatening sepsis or organ dysfunction or poor long-term functionality of the limb [105–107]. A scoring system was devised by Johansen et al. that has gained popularity and is termed the mangled extremity severity score (MESS) [105]. Amongst patients with a high (>7) MESS score, vascular and neurolgic deficits are common, and these patients have higher rates of non-functional extremities if they survive [105]. In turn, non-functional extremities portend an inferior quality of life and overall functionality when compared to an amputated limb followed by prosthesis and rehabilitation [106–110]. Moreover, limb salvage in severely injured extremities such as Gustilo Type IIIB and IIIC fractures of the tibia is often associated with significant complications such as infection, nonunion, failure of soft tissue coverage, and eventual requirement for delayed amputation as described in a systematic review by Saddawi-Konefka et al. [111]. The rate of delayed or secondary amputation amongst patients undergoing extensive limb salvage efforts has been reported to be as high as 25% [112]. The functional outcome of patients undergoing early amputation tends to be improved with respect to both extent and rate. In a study by Barla et al., patients undergoing primary (or early) amputation were able to walk for longer distances and with fewer gait aids, with higher functional recovery scores [113, 114]. A limb that is non-functional, painful, or septic is inferior to amputation followed by prosthesis [110]. In this fashion, early amputation can serve as prophylaxis against prolonged morbidity given appropriate patient selection. Prioritization

of life over limb dictates that there are specific circumstances based on patient and injury specific factors where prophylactic amputation is the preferred approach. Surgical decision making in the form of risk stratification, physiologic monitoring, and a proactive approach are paramount in maximizing benefit over harm in the setting of prophylactic limb sacrifice.

24.10 Conclusion

Management of trauma patients is complex and may involve seemingly prophylactic procedures. Unfortunately, a "one size fits all" approach that may be appropriate in other surgical disciplines does not hold true for trauma patients as the mechanism of injury, patient anatomy, and physiology make each patient unique. As demonstrated, there are no definitive algorithms or protocols to guide surgeons in their decision-making process while managing these subsets of patients; only recommendations based upon prior experience and clinical research. Clinical judgement will dictate modification of recommendations and a comprehensive review of the patient's injuries, medical comorbidities, and an understanding of their physiologic state is of utmost importance in selecting the ideal candidates for prophylactic surgical intervention.

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Surgical Prophylaxis of Obesity

25

Erdinc Kamer and Fevzi Cengiz

25.1 Introduction

Obesity is a condition where body fat mass exceeds normal acceptable levels and it is a chronic metabolic disease with high mortality and morbidity rate due to metabolic complications. The World Health Organization (WHO) has defined the term "obesity" as excessive fat accumulation that is harmful to health. Obesity, considered as the twenty-first century's epidemic, is the primary health problem in developed countries, reducing life expectancy and creating a challenge for the global economy. WHO has defined obesity as a disease in ICD-10 [1, 2]. Obesity is usually defined by the Body Mass Index (BMI) criteria, which is obtained by dividing body weight in kilograms by the square meter in meters. According to the BMI, individuals are divided into five different categories: (1) 18.5–24.9 kg/m^2 is classified as healthy or normal, (2) 25.0–29.9 kg/m^2 as overweight, (3) 30–34.9 kg/m^2 as class 1 obesity, (4) 35.0–39.9 kg/m^2 as class 2 obesity, (5) ≥40 kg/m^2 as class 3 obesity (Table 25.1) [3]. Those with the highest risk in terms of obesity-related consequences are the individuals with BMI ≥40 kg/m^2 in the group defined as morbid obese. More than 35% of adults are obese in the United States and Turkey [4]. According to the "Turkey Nutrition and Health Survey-2010" preliminary studies report issued by the Ministry of Health of the Republic of Turkey, the prevalence of obesity is 30.3% [5].

Table 25.1 Indications for bariatric surgery [3]

1.	If BMI is ≥40 kg/m^2, there is no additional comorbidity requirement related to obesity; surgical treatment should not cause increased risk.
2.	If BMI is ≥35 kg/m^2, at least one comorbidity associated with obesity should be accompanied. These associated situations are as follows: (a) Type 2 diabetes mellitus (b) Hypertension (c) Dyslipidemia (d) Sleep-apnea syndrome (e) Obesity-hypoventilation syndrome (f) Pickwick syndrome (coexistence of sleep-apnea syndrome and obesity-hypoventilation syndrome) (g) Non-alcoholic fatty liver disease or "non-alcoholic steatohepatitis (NASH)" (h) Pseudotumor cerebri (i) Gastro-esophageal reflux disease (j) Asthma (k) Venous stasis disease (l) Advanced urinary incontinence (m) Arthritis affecting daily life

Increased prevalence of obesity causes an increase in various comorbidities especially in type 2 diabetes, cardiovascular and cerebrovascular diseases, digestion, leukomotor and respiratory disorders, cancers (such as colon, breast and uterus), and psychosocial complications [6]. If overweight and obesity continue with this rate, it

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is reported that it will affect 60% of the world population in 2030 (2.2 billion overweight, 1.1 billion obese, 89% male, 85% female) and result in an increase by 97% in obesity-related heart disease prevalence, by 61% in cancer prevalence and by 21% in Type 2 diabetes prevalence [7, 8]. On the other hand, the prevalence of overweight and obesity among children and adolescents has started to increase worldwide. WHO European Childhood Obesity Surveillance Initiative (COSI) routinely measures the overweight and obesity prevalence of children aged 6–9 years, and according to these data, the prevalence of obesity was found to be between 6.0–26.6% in boys and 4.6–17.3% in girls. Overweight among children of 6–9 years is defined as a serious public health problem [9].

While obesity causes serious health problems on the one hand, it causes significant economic impact on the other. The cost of obesity complications and treatments in the United States is approximately $200 billion, accounting for over 20% of all US healthcare spending in 2005. The global economic impact of obesity was estimated at $2.0 trillion in 2014 [10].

25.2 Obesity Comorbidities

The incidence of many chronic diseases has increased in obese people. These risks are higher for class 3 obese individuals, whose BMI is over 40 kg/m^2. Obesity is the cause of increased mortality independent of concomitant diseases. Diseases accompanying obesity and complications of obesity are: diseases related to the cardiovascular system (hypertension, atherosclerotic heart and myocardial infarction and cerebral vascular accidents and peripheral vascular disease, peripheral venous insufficiency, thrombophlebitis, pulmonary embolism), respiratory system related diseases (obesity-hypoventilation syndrome, obstructive sleep apnea, dyspnea), diseases related to the metabolic-endocrine system (Type 2 diabetes mellitus, dyslipidemia, insulin resistance), diseases related to the gastrointestinal tract (Hiatus hernia and reflux disease, nonalcoholic fatty liver, hepatic cirrhosis, hepatic carcinoma, gallstones, colectal cancer), diseases related to neurological diseases (nerve compression, carpal tunnel syndrome, sciatica, pseudotumor cerebri), musculoskeletal system (osteoarthritis, flat foot, disc diseases), endocrine and genitourinary system related diseases (stress incontinence, decreased fertility, mechanical difficulty in sexual intercourse, pregnancy complications, urinary stones, polycystic ovarian syndrome, male hypogonadism, endometrium, breast, ovarian, prostate and pancreatic cancers), related to psychosocial conditions (self dissatisfaction, depression, anxiety, difficulty in finding work, high life insurance premiums, unhappiness in marriages, eating disorders), dermatology related diseases (intertriginous dermatitis). Approximately 30% of overweight adolescents in the United States (USA) meet metabolic syndrome criteria, which increases the risk of type 2 diabetes and coronary heart disease. Obesity ranks second as a preventable cause of cancer in the USA. Obesity causes 40% of the cancers diagnosed to develop in the USA [11]. The International Agency for Research on Cancer-OAC has identified 13 malignancies including obesity-related post-menopausal breast, colorectal, kidney, endometrial, thyroid, pancreas, liver, gastric cardia, meningioma, ovarian, esophageal adenocarcinoma, gallbladder and myeloma malignancies [12]. The effect of obesity on long life is well documented. More than 2.5 million deaths per year can be attributed to obesity worldwide [13].

25.3 Patient Selection and Targets

The aim of obesity treatment is to impose adequate and balanced eating habits and to improve the quality of life by targeting the individual specific body weight loss in order to reduce obesity-related morbidity and mortality risks. Treatment options for obesity include surgical treatment and non-surgical treatment. Non-surgical treatments include dietary changes, use of various pharmacological agents, physical exercises, and behavioral therapy methods. The first-line treatment of obesity should be diet and lifestyle changes. If

these are not successful, drug treatments are added. Unfortunately, in obese patients, most of these can be ineffective in ensuring and maintaining weight loss. Therefore, the use of bariatric surgery methods in morbid obesity is increasing worldwide. Studies have shown that surgical methods in obesity treatment lead to more effective and permanent weight loss in the long term compared to non-surgical methods [14]. Therefore, the use of bariatric or metabolic surgical methods is increasing worldwide. In 2013, 468,609 cases were reported worldwide, with 154,276 cases in the USA/Canada and 3250 cases in Turkey [15, 16]. It is seen that these numbers have increased considerably today.

The principles of the National Institutes of Health (NIH) adopted in 1991 are generally accepted as the basis for patient selection for bariatric surgery. General indications are shown in Table 25.1. In addition to those, they can be listed as failure in medical treatments applied prior to surgical treatments, stability of the psychological state, presence of family and environmental support, no alcohol and drug addiction, and fully informing the patient about the application [17].

25.4 Surgical Techniques

The bariatric surgery methods used includes "Absorption Degrading Methods" such as biliopancreatic diversion (BPD), jejunoileal bypass (JIB), which cause weight loss by shortening the length of the small intestine where absorption takes place, by bypassing the area where absorption takes place and preventing the encounter with biliopancreatic secretions that play a role in absorption, "Intake Restriction Methods" such as Sleeve gastrectomy (SG), adjustable gastric band (AGB), vertical band gastroplasty (VBG) that provides weight loss by reducing food intake by reducing gastric volume and Roux-en-Y gastric bypass (RYGB) performed by combining these two methods, biopancreatic diversion ± duadonal Switch (DS) and mini-gastric bypass. Among many different (over 50) effective surgical methods used for treating obesity, most of the popular bariatric procedures such as Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), mini-gastric bypass, and biopancreatic diversion (BPD) are considered as the safest effective procedures in terms of obesity-associated comorbidities and weight loss [2, 18].

25.5 Prophylactic Surgery and Outcomes

Prophylactic surgery is not a very new concept. The purpose of prophylactic surgery is to prevent the development of the disease. Patients usually leave therapeutic surgery because it is asymptomatic and surgery is not required immediately. Prophylactic surgery can be performed in individuals who are prone to develop cancer from the hereditary mutations most frequently diagnosed by genetic testing, as well as for all organs foreseen to develop the disease. Although bariatric surgery operations are procedures to protect the patient from possible diseases and complications in the future, it has not been defined as a prophylactic surgery procedure. There are very few articles in the literature that describe this as a prophylactic procedure [19].

Bariatric surgery operations are applied to patients for metabolic surgery as well as surgeries that result of weight loss. In the foreword part of the Metabolic Surgery book dated 1978, the discipline of bariatric surgery has defined metabolic surgery as "operational manipulation of a normal organ or organ system to achieve a potential health gain and get a biological result." In Genesis, metabolic surgery has been described as an "operative manipulation" under general anesthesia on "normal organ" to achieve a "biological result" [20].

Various surgical procedures, generally used in bariatric surgery, result in approximately 34–85.3% partial or total T2D remission depending on criteria applied to define Type2 DM (T2D) remission and 95% global success in glycemic control [21]. RYGB is also a very effective option for T2D remission. Most patients who were applied RYGB did not require drug use 1 year after surgery and T2D remissions of 84–90% and 29–50% were reported respectively 1 and 5 years

after RYGB [2]. However, T2D remission rates vary in the literature. Yan et al. had reported 56.81% (36.8–90.3%) T2S remission, while Chang et al. reported 95.15% (88.38–98.8%) [22, 23]. Sleeve gastrectomy has gained popularity in recent years due to glycemic control rates similar to RYBG and lower complication rates related to surgery. In the study of the Swiss Multicenter Bypass or Sleeve Study (SMBOSS), which was a randomized controlled study, T2D remission rates were shown as 60% in SG and 77% in RYGB 3 years after the surgery [24]. It has been reported that laparoscopic mini-gastric bypass provides successful remission in patients with BM2 > 35 and 77% in patients with BMI <35 in T2D/impaired fasting glucose patients [25]. Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) Trial in a study comparing 150 patients with T2D in terms of bariatric surgery (SG and RYGB) and medical treatment, more weight loss, normalization of glycine hemoglobin, decreased triglyceride levels, reduction in high density lipoprotein levels, and decrease in the use of insulin and other antidiabetic agents were seen more compared to the medical group. In addition, a reduction was observed in the use of lipid lowering or antihypertensive in bariatric patients [26]. Brolin et al. reported in their study that, considering that presence of at least one concomitant disease related to obesity is known in 95% of the patients over 45 and who had undergone bariatric surgery, it was obvious that the future development of diseases such as T2D (very likely in case of family history), hypertension, and hyperlipidemia could be prevented by the bariatric surgery to be applied to these patients who do not have any additional disease other than obesity [27].

Obesity is known to have risk and negative consequences for increased cardiovascular diseases (CVD). A significant improvement was observed in cardiovascular risk factors such as hypertension, dyslipidemia, and T2D after bariatric surgery with the ratios of 63%, 65%, and 72%, respectively [28]. This wide improvement in cardiovascular risk factors led to a significant reduction in the risk of stroke, myocardial infarction, and death [29]. Many studies clearly show that obesity is an independent risk factor for early CVD morbidity and mortality in childhood and adolescence [30]. Also, the steady increase in obesity prevalence causes an increase in CVD risks in young people with obesity. On the other hand, it is useful to examine the economic damage caused by long-term CVD risk with obesity treatment. Ryder et al. showed in their study that adolescents with severe obesity were at high risk for CVD within 30 years, the postoperative MBIs of adolescents who had undergone bariatric surgery significantly reduced the risk of CVD despite having a plateau after a while, and that bariatric surgery was cost-effective as it prevented CVDs and CVD related early mortality in adolescents with obesity [23]. Therefore, prophylactic bariatric surgery can be considered in adolescents without CVD to reduce both the risk of developing CVD and mortality from CVD at a later age.

Given the multiple mechanisms by which obesity increases the risk of cancer, it is possible to see that some types of cancer decrease with bariatric surgery [31]. In general, bariatric surgery reduces the risk of cancer in women by 42%, while cancer risk in men has not been reduced [32]. For example, it is known that breast and endometrium cancers are very sensitive to estrogen levels and patients have a history of exposure to estrogen in their etiology and a decrease in the incidence of these two cancers after menopause [32]. Since it has been shown that weight loss reduces the circulating estrogen level and reduces the risk of breast and endometrum cancer, it is obvious that bariatric surgical interventions that will be performed before seeing cancer in obesity patients will provide a prophylaxis for this cancer due to weight loss that takes place with bariatric surgery [33]. In addition, in a study in which bariatric surgery was performed with gastric bypass and sleeve gastrectomy, it was reported that there was a decrease in the risk of esophageal adenocarcinoma in the group that had undergone bariatric surgery [33]. A decrease in the risk of colon cancer was also detected in the group treated with bariatric surgery in the same study [33]. As a result, since bariatric surgery decreases the risk of breast, endometrium, esophagus and colon

cancer, application of bariatric surgery to obese patients may create a prophylaxis.

There is a relationship between BMI and physical limitation and fatigue. In other words, obesity is closely related to the decrease in a person's health-related quality of life. At the same time, psychosocial problems such as dissatisfaction with their body appearance, unhappiness in their marriages, and difficulty in their sexual lives are more common in these individuals compared to the normal population [34]. In studies conducted in our country, it has been revealed that psychiatric disorders are also common in obesity patients. Eren and Erdi reported in their study that 81.3% of obese patients who applied to the endocrinology department for treatment purposes had major depressive disorder, 71.7% had major depressive episodes in the last month, and other psychiatric distribution distributions were reported to be 22.6% social phobia, 17% nicotine addiction, 5.8% alcohol dependence 5.7% anxiety disorder, and 3.8% obsessive compulsive disorder, respectively [34]. Considering that 81.3% of obese patients had major depressive disorder and 71.7% of them had a major depressive attack in the last month, the rate of encountering psychosocial problems in their future life is quite high for an obese patient. Prophylactic bariatric surgery to be performed has important psychosocial effects on individuals. Approximately 40% of patients who request bariatric surgery present with at least one mental health condition such as depression, anxiety, overeating disorder, and alcohol use disorder or impulse control disorders [35]. There is a lot of evidence that bariatric surgery has a positive effect on psychopathology, quality of life, body appearance, socio-economic status, and social relationships [36–38]. Therefore, in order to prevent this, prophylactic BS may be considered for obese patients.

25.6 Conclusion

Considering that bariatric surgery increases the quality of life in obese patients and reduces or eliminates comorbid medical problems and given the advantages and disadvantages gained, it is seen that operations performed for obesity are prophylactic applications, even if they are not defined as prophylactic surgery. Nevertheless, as a concept that has not been widely used in the literature, we believe that surgical practices in obesity are performed for prophylactic purposes and it will be useful to examine the issue in terms of ethics, medicine, and cost.

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26 Histopathological Findings in Prophylactic Surgical Specimens

Fatma Hüsniye Dilek and Dilara İrem Arslan Kahraman

26.1 Introduction

Over the past few decades, the expansion of familial cancer registries and advancement in genomics have led to the development of clinical diagnostic criteria for specific hereditary syndromes as well as the discovery of multiple genes in which germline mutations predispose individuals to syndrome-associated neoplastic manifestations [1, 2]. The number of specimens that have come up as a result of treatment with prophylactic surgery has been increasing in recent years and many studies on the subject are entering the literature. The early onset is still one of the most important and relatively specific features of most of hereditary cancer syndromes. Multifocal involvement is a characteristic but insensitive clinicopathological feature of these syndromes. In recent years, it has been illustrated that a significant proportion of hereditary neoplasia displays distinctive or unusual histopathological and/or immunophenotypic features. In addition, these features are useful to better understand the phenotype and biology of the disease. We summarize the current knowledge about diagnostic features and morphological alterations in specimens from therapeutic/prophylactic surgery of some diseases.

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26.2 Hereditary Diffuse Gastric Cancer

Ten percent of all gastric cancers show familial clusters, whereas 1–3% are hereditary [1–4]. Hereditary diffuse gastric carcinoma (HDGC) is an autosomal dominant syndrome, mainly caused by a germline mutation of the CDH1 gene, with a risk of developing diffuse-type gastric cancer and invasive lobular cancer [4, 5]. The CDH1 gene encodes E-cadherin which is an adhesion molecule and functions as a suppressor gene that regulates cell proliferation [6, 7]. The age of symptomatic gastric cancer in patients who were born with the CDH1 mutation is very variable (14–85) and the mean age is 38 [3–5, 8–10]. Women have an additional 40% risk for lobular breast carcinoma [1, 5].

Very few of the families with HDGC have a germline CTNNA1 mutation. CTNNA1 encodes the α-catenin protein, which plays a role in cell adhesion and E-cadherin binding by forming a complex with B-catenin [5, 11]. It is stated that in those carrying CTNNA1 mutation precursor lesions and lobular breast cancer typical of CDH1 mutation are not observed [1, 3, 5, 11–14].

Detailed and comprehensive screening protocols with annual endoscopic surveillance are

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recommended in asymptomatic CDH1 carriers [12, 14, 15]. However, the sensitivity of endoscopy is not perfect in determining early-stage carcinoma foci. Even in intensive endoscopic follow-ups, the rate of detection of cancer focus in biopsy is reported low [16]. Since early-stage carcinoma focus usually spreads under the intact mucosa, it usually does not form macroscopic changes [12, 17, 18]. It may create inconspicuous, pale, little foci, and be overlooked in endoscopy [12, 19–21].

The cancer focus rate determined in some prospective studies using the Cambridge endoscopy protocol proposed by IGCLC (The International Gastric Cancer Linkage Consortium) guidelines was reported as 61.1% and 63.6% [19, 22]. With endoscopic follow-up, early carcinoma focus cannot be detected in approximately 40% of the patients [9]. Prophylactic/risk-reduction total gastrectomy is the treatment option because intense screening protocols are insufficient in detecting intramucosal carcinoma in those with CDH1 mutation [5, 8, 15, 18]. In patients who did not have surgery, detailed endoscopic follow-up with white light, high definition endoscope, and multiple endoscopic biopsies are recommended in expert centers [3, 5, 15, 16, 23].

Gastric cancer seen in CDH1 mutation carriers is a poorly cohesive, diffuse carcinoma with signet cell morphology [22, 24]. The phenotype, the number, or the localization of HDGC carcinoma foci determined by the type of germline CH1 mutation is irrelevant. The age of onset of the clinical disease is unpredictable; however, the number and the diameter of cancer foci detected in gastrectomy specimens are not related to age [3, 9, 22, 25].

Four morphologies have been described for CH1-related gastric cancer and its precursor lesions [1, 3, 8, 9, 17, 26, 27].

Signet-Ring Cell Carcinoma (SRCC) In Situ (pTis): The presence of atypical signet-ring cells with hyperchromatic nucleus pushed to one side of the cytoplasm that replace normal epithelial cells within the basal membrane of the gland.

Pagetoid Spreading of Signet-Ring Cell Carcinoma (pTis): The arrangement of the signet-ring cells in a row within normal gastric glands and between the foveolar epithelium and the basal membrane.

Intramucosal (pT1a) SRCC); Invasive carcinoma limited to the mucosa, consisting of signet-ring cells, invasive to lamina propria.

Advanced Diffuse Hereditary Gastric Carcinoma: Poorly cohesive carcinoma that has minor SRCC component as advanced (pT1) and sometimes has a precursor or pT1a SRCC component around.

HDGC and sporadic diffuse gastric cancer (SDGC) are indistinguishable macroscopically and microscopically [1, 28]. Although morphologically similar, HDGC and SDGC are different histologically, immunohistochemically, and may have different carcinogenetic pathways [12, 24, 29]. Signet-ring cell carcinoma in situ and pagetoid spread of signet-ring cells are specific to HDGC with CDH1 mutations. It has not been reported in SRCC without germline CDH1 mutations [3, 8, 17].

Advanced HDGC has no specific and characteristic morphological features. It is mostly characterized by diffuse infiltration of the pleomorphic neoplastic cells in the gastric wall. The gastric wall looks thickened and stiff (linitis plastica). Sometimes tumor cells can form small aggregates, rosettes, or gland-like structures. Classic signet-ring cells may not be seen or they may form a subset of the tumor. An infiltration completely or predominantly consisting of signet-ring cells can also be seen and extracellular mucin can be found. In situ lesions seen around the tumor and pagetoid spread of signet-ring cells are important clues for HDGC [1, 3, 27, 28].

Updated clinical guidelines generally recommend a total examination of the prophylactic gastrectomy specimens of asymptomatic CDH1 mutation carriers because there is no gross lesion and to determine the patient's stage and to understand the biology of the disease [3, 7, 17, 28]. Gross digital photographic documentation is required to map the stomach and record localizations [3, 28]. Accordingly, the stomach is taken for microscopic evaluation in total. Alternatively, the Swiss roll technique may be used [3, 30].

With the histological examination of the gastric mucosa, it is seen that almost all gastrectomy

specimens often have numerous microscopic (0.1–10 mm), intramucosal (pT1a) signet-ring cell carcinoma foci, and precursor lesions [1, 9, 16–20, 26, 31, 32]. If the total-embedding protocol is applied, the number of precursors or invasive carcinoma foci that identify the lesion is significantly increased. Literature reviews revealed microscopic signet-ring cell carcinoma in more than 95% of the prophylactic gastrectomies in which total-embeddig protocol was applied, and 62.5% of those who did not [3, 5, 9, 28]. Intramucosal signet-ring cell carcinoma foci can be seen in all stomach regions. In theory, signet-ring cell carcinoma can develop from any metaplastic or heterotopic gastric mucosa. For this reason, surgical removal of the entire gastric mucosa, histological examination of all stomach areas, and surgical margins (complete cuff of squamous esophageal and distal duodenal mucosa) are recommended [1, 3, 16–18, 20, 26, 28, 31].

In prophylactic gastrectomy specimens, lymphocyte gastritis, tufting in the surface epithelium, and changes such as globoid change, vacuolization, and foveolar hyperplasia have been described. However, these are not considered as specific findings. Intestinal metaplasia and *H. pylori* infection are generally absent [3, 27, 30].

Caution should be taken in the identification of signet-ring cells and distinguishing between signet-ring cell-like benign changes [3, 9, 17, 27]. Biopsy and surgical specimens should be carefully evaluated by a pathologist experienced in HDGC pathology [1, 3, 9]. Biopsies should be stained with three levels of H&E and periodic acid–Schiff-diastase (PAS-D) as a standard [3]. The signet-ring cells in the lamina propria can be easily distinguished with PAS stain with their cytoplasm stained magenta, this way the number of small carcinoma foci that are overlooked reduces [3, 9, 17, 24, 27, 33].

E-cadherin expression is usually aberrant in HDGC and its precursor lesions. Immune expression of E-cadherin is in the form of absence or reduction of membranous (normal staining pattern) staining. Cytoplasmic or dotted staining can also be seen [12, 17, 20, 27, 34]. Depending on the germline mutation type, sometimes the immunohistochemical expression of membranous E-cadherin can be seen [3]. The expression of abnormal E-cadherin can also be seen in SDGC. Therefore, the immunosuppression of E-cadherin is unreliable in the diagnosis of HDGC [12].

Recent studies suggest that HDGC is progressive through many phases [24]. In some prophylactic/risk-reducing gastrectomies, the intramucosal signet-ring cell carcinoma focus is not found adjacent to the in situ component. The presence of a large number of T1a carcinoma foci and the lack of accompanying in situ carcinoma suggests that invasive carcinoma may develop without a detectable in situ focus [17, 24].

In asymptomatic CDH1 mutation carriers, intramucosal signet-ring cell carcinomas are thought to remain indolent for a long time. No lymph node metastases and distant metastases have been reported in these cases [3, 17]. It cannot be foreseen how long it will take the precursor lesion or intramucosal carcinoma focus to develop into an advanced carcinoma [1, 9, 12, 29, 32].

Many studies are being conducted to understand how carcinogenesis develops in CDH1 mutation and to predict the aggressive course. Most of the pT1a foci show the morphology of very few mitotic cells and the low proliferation of the Ki-67 index [12, 20, 34]. Advanced HDGC has an aggressive phenotype. The Ki-67 proliferation index is high. P53 expression is seen. It has been suggested that P53 mutation may be important in the progression of carcinoma [1, 3, 12, 24, 27, 28]. In another study about CDH1-mutated gastric cancers, it was shown that C-Src kinase which is considered as the inducer of ependymal mesenchymal transition, was expressed in the cells that are poorly differentiated and that have invaded the muscularis mucosa whereas there was no expression in intramucosal signet-ring cells [34].

Some researchers have identified the cells of different phenotypes in prophylactic/risk-reduced gastrectomy specimens. Large cells (mucin-rich) with abundant mucin, eccentrically located, and flattened nucleus, low nucleus cytoplasm ratio

are mostly superficially located under the surface epithelium. Small cells with a high nucleus/cytoplasm ratio have less mucin, with a more rounded hyperchromatic and atypical nucleus (mucin-poor). They are located in the neck region [1, 3, 16, 17, 29]. In their recent studies, Lee et al. [29] showed that large cells (well-differentiated) were rarely positive for mucicarmine, and immunohistochemically positive for pCEA and negative for CDX2, whereas small cells (poorly differentiated) were positive for mucicarmine and pCEA, and negative for CDX2. Large cells were identified as well-differentiated cells and small cells were identified as poorly differentiated cells. The authors also described a different group of cells within poorly differentiated small cells, which are pleomorphic small cells with large atypical nucleus and intense pink cytoplasm that do not contain mucin. These cells are negative for mucicarmine and they show strong expression of p16 immunohistochemically. They do not show immunoreactivity for CDX2 and pCEA. It has been suggested that aberrant p16 expression may be a progression indicator of the disease [29].

HDGC is a heterogeneous disease with great variability in clinical behavior, morphologic appearance, and immunophenotypic and molecular profile. There is a need for studies that will enable us to predict the age of development of carcinoma in those carrying the CH1 mutation, why some carcinomas are more indolent, some are aggressive, and what the factors are that provide an aggressive outcome. Involvement of a full multidisciplinary team is essential for the management of the patients.

26.3 Lobular Breast Carcinoma

The indicators of molecular changes in all lobular carcinomas are atypical lobular hyperplasia, lobular carcinoma in situ, and invasive lobular carcinoma. During these changes, cellular adhesion decreases and E-cadherin expression decreases or disappears. In patients with CDH1 mutation, there are no large series of histological findings since prophylactic mastectomy is not usually preferred in patients. A small number of reported studies with prophylactic mastectomy, histopathological findings different from solitary lobular carcinoma/lobular carcinoma in-situ were not reported. These mastectomy specimens were generally not fully embedded and examined [3, 24]. Kluijt et al. [30] defined bilateral multifocal lobular carcinoma in situ foci in two female patients that underwent prophylactic mastectomy [30]. In one study, CDH1 germline mutation has been shown in up to 8% in patients with bilateral lobular carcinoma in situ [35].

26.4 Multiple Endocrine Neoplasia

Multiple endocrine neoplasia (MEN) syndromes are the appearance of neoplasms in two or more endocrine organs. This syndrome shows autosomal dominant transition and is divided into four types today [36–38]. In MEN1 (or Wermer) syndrome, the product is due to the germline mutation of the MEN1 gene, which is menin. Neuroendocrine tumors in the pancreas and anterior pituitary, parathyroid, and adrenocortical tumors are seen [38].

MEN2 (or Sipple's) syndrome is the result of a RET proto-oncogene germline mutation encoding a transmembrane tyrosine kinase receptor [39]. There are three clinical variants: MEN2A, MEN2B, and Familial MTC (FMTC). In MEN2A, medullary thyroid carcinoma (MTC), parathyroid tumors, and adrenal medullary pheochromocytoma develop. MEN2B (MEN3 or Wagenmann–Froboese syndrome) is characterized by medullary thyroid carcinoma, pheochromocytoma, mucosal neuromas, and intestinal autonomic ganglion tumors, with marfanoid appearance [36–38]. In the familial medullary thyroid carcinoma of the MEN2A variant, the only or the first symptom of the syndrome is seen as medullary thyroid carcinoma [36, 40]. Recently, the new MEN type has been defined as MEN4. This type is due to the mutation in CDKN1B (encodes p27, a cyclin-dependent kinase inhibitor) gene, and patients have anterior pituitary and parathyroid tumors [36].

The specific codons of the mutation in the RET gene are associated with the risk of carcinoma. The MTC seen in MEN2 is age and mutation-specific, while in MEN2B it is mostly seen in early childhood; in MEN2A it is seen at an average of 25–35 years Therefore, according to the international guidelines, prophylactic thyroidectomy is recommended in families with MEN2B and FMTC at an early age [40–42].

26.4.1 Medullary Thyroid Carcinoma

Medullary carcinomas arise from the junction of the medium 1/3 of the lateral lobes and the upper lobes where the C cells which they originate from are localized. C cells are normally distributed individually and cannot be easily seen morphologically, and may require immunohistochemical staining [43]. C cell hyperplasia (CCH) is seen as clusters formed by large, spindle, columnar or plasmacytoid-looking basophilic granular cells. Not all C cell hyperplasia is a precursor lesion for MTC, since this entity can also be a reactive condition associated with other thyroid pathologies [43]. The progression of C cell hyperplasia to a tumor with aging is an important feature of hereditary MTCs [44]. The CCHs, which are associated with the RET mutation and are considered precursors, are called neoplastic CCHs. It can be defined as the presence of more than 50 C cells in the small magnification area containing more than six to eight C cells in each cluster in the densest area [44]. Nodular or neoplastic CCH are defined as solid aggregates in follicular spaces that are proliferated from amphophilic C cells [43–46]. Neoplastic CCH can be easily noticed in HE staining without counting. These cells are often large and show significant nuclear atypia [43, 44]. Such proliferations can be difficult to separate from micromedullary carcinoma (tumors of 1 cm or less in size) or intrathyroidal spread of an existing medullary carcinoma [40, 43–47].

Medullary carcinomas have characteristic morphology similar to neuroendocrine tumors that appear as solid or nested. The appearance of amyloid due to procalcitonin storage is characteristic. Sometimes the diagnosis may need to be confirmed with immunohistochemical stainings such as chromogranin, calcitonin, and CEA since unusual different morphologies can be seen [43]. Unlike solitary tumors, MEN-related tumors are usually bilateral, multiple, and show multifocal neoplastic CCH. For this reason, careful macroscopic evaluation of the whole organ in resection materials and sampling of all are recommended [43, 46].

26.4.2 Parathyroid

Hyperparathyroidism occurs in more than 90% of MEN-1 [48–50]. Unlike sporadic ones, hyperparathyroidism is seen equally in men and women and has multiple gland involvement. Histological changes of parathyroid of MEN1 and MEN4 are similar [46, 49, 50]. All glands have mild to moderate growth, whereas sometimes one or more glands show marked growth. (Its size is bigger than 6–8 mm and its weight is more than 40–60 mg.) The hyperplasia caused by the chief cell proliferation that causes the growth can be predominantly diffuse, nodular, or diffuse/nodular [49, 51, 52]. Sometimes one gland can contain more than one nodule. Histologically, sometimes it is very difficult to distinguish between normal/hyperplasia or hyperplasia/adenoma. Unlike sporadic adenomas, the atrophic rim is not seen in non-lesional parathyroid tissue. Therefore, the cause of hyperparathyroidism in MEN syndrome has been defined as "multiglandular parathyroid disease" [46, 48, 53]. Recent molecular studies suggest that this is multiple multiglandular microadenomas caused by multiple monoclonal (708,728,896) proliferations [49, 50]. Unlike MEN1-related primary hyperparathyroidism, MEN2A syndrome often presents with single gland involvement that is indistinguishable from sporadic parathyroid adenoma at the morphological level [49, 50, 53]. MEN-related parathyroid neoplasms show benign behavior. Parathyroid carcinoma is very rare [48–54].

26.4.3 Pancreas

Forty percent of MEN-1 patients show symptoms of Zollinger–Ellison syndrome developing due to the tumors secreting multifocal gastrin. Gastrinomas are mostly smaller than 1 cm and tend to occur as multiple lesions in the duodenal submucosa and less commonly in the pancreas in MEN1 patients [44, 55]. Pancreatic islet neuroendocrine tumors (NETs) are the second commonest manifestation of MEN1, occurring in up to 80% of patients [36]. Pancreatic NETs are multiple and occur throughout the head, body, and tail of the pancreas and range from microadenomas, to macroadenomas, to invasive and metastatic carcinomas. The criteria that define the risk for metastasis are probably the same as in sporadic tumors. Compared with their sporadic counterpart, some MEN1-associated pancreatic NETs exhibit a more aggressive potential behavior [1, 55]. The functional tumors seen in the pancreas are usually NETs that produce insulin and are seen at an earlier age than the sporadic ones, and behave more aggressively [44].

In MEN-1, one or more neuroendocrine tumors are seen in the pancreas and this is a feature of the associated "diffuse microadenomatosis" syndrome. Islet dysplasia and microadenomas are considered as precursor lesions [1, 56]. Ductulo-insular complexes (nesidioblastosis) and peliosis that are seen in non-tumor islets are important non-specific histological findings of MEN [44, 57, 58].

The cells of the normal islet that contain glucagon surround the cells of the tubules that form insulin-producing solid tubules. The cells that contain somatostatin were randomly distributed. Disruption of the normal quantitative and qualitative distribution of alpha, beta, gamma, and delta cells defines the concept of islet dysplasia. Dysplastic islet consists of normal or slightly enlarged cells containing minimal cytological atypia [44, 58, 62]. When the size of the dysplastic islets reaches 0.5 mm, it is defined as microadenoma or microNET [44, 57, 58]. Microadenomas are numerous (diffuse microadenomatosis) and often non-functional. If the size of the microadenomas is larger than 5 mm, it is called a neuroendocrine tumor (NET). Most MEN-related NETs are Grade 1 or Grade 2 well-differentiated neuroendocrine tumors. Immunohistochemically, most tumors are multihormonal, but typically one hormone predominant. This hormone is also often glucagon [50, 62].

26.4.4 Adrenal Gland

Adrenal pathology is found in 20–25% of MEN-1 patients [59]. The most common adrenal lesion in MEN 1 is bilateral macronodular adrenal cortical hyperplasia, while adenomas are seen secondly, and cortical carcinomas are rare [60]. Tumors are often smaller than 3 cm and non-functional [2, 61].

Pheochromocytomas seen in MEN2 are almost always benign. Unlike solitary tumors, it is accepted that they develop from medullary hyperplasia, which is considered as a precursor lesion [2, 44, 61–63]. Adrenal medulla shows nodular and/or diffuse growth. Sometimes it may be difficult to recognize medullary hyperplasia morphologically. The presence of the medulla in the caudal part of the organ where it is not normally found and the medulla forming more than 1/3 of the organ thickness, suggest medullary hyperplasia [44, 51]. It may not be possible to separate nodular hyperplasia from pheochromocytoma [61–64]. Also, nodular hyperplasias that are seen in MEN2 show monoclonality. Therefore, it is recommended to use the term "microphaeochromocytoma" instead of nodular hyperplasia [62, 64]. Practically, nodules of 1 cm and larger are considered as pheochromocytoma [63]. In the MEN2, medullar nodules and pheochromocytoma can be seen without hyperplasia on the background [44]. The pheochromocytomas show the same characteristics as those seen as morphological and immunohistochemically solitary [61, 63].

26.4.5 Pituitary Gland

Lactotroph adenomas are the most common of MEN-1 and MEN-4 associated pituitary

adenomas. Second, non-functional adenomas are seen [2, 65]. Adenomas seen in MEN-1 are often multiple, and multihormonal compared to sporadic cases, and the majority are large (macroadenoma) [65]. Ki-67 proliferation index is higher and shows more frequent invasive features [65–67]. The risk of progression/recurrence is high, but the risk of pituitary carcinoma is not increased compared to the general population [68].

In MEN syndromes, endocrine neoplasms are mostly multifocal and are associated with precursor lesions [2, 68]. For this reason, it is recommended that careful morphological examination of tumors and non-tumoral parenchyma of the affected organ and examination of the entire resection are recommended.

26.5 Lynch Syndrome

Lynch syndrome (LS) is an autosomal dominant cancer predisposition disorder that is caused by germline mutations in the DNA mismatch repair (MMR) genes MLH1, MSH2, MSH6, and PMS2, or by germline mutations in EPCAM which lead to epigenetic methylation and silencing of the MSH2 gene [69–72].

The term hereditary non-polyposis colorectal cancer (HNPCC) previously used interchangeably with Lynch syndrome; however, these two conditions are not synonymous. HNPCC is a clinical term for patients with carcinoma that fulfill Amsterdam clinical criteria that are based on family history [1, 73, 74]. Approximately 40% of patients with HNPCC do not harbor MMR protein deficiency within their tumor or have a germline DNA MMR gene or EPCAM alteration. HNPCC conditions with intact DNA MMR associated with familial CRC include polymerase proofreading associated polyposis and familial colorectal cancer type X (FCCTX). Patients with FCCTX do not have an increased risk for extracolonic cancers [71, 75, 76].

Lynch syndrome can be identified in 2–3% of all colorectal cancer (CRC) patients, and approximately 2% of all endometrial cancer patients. There is also an increased risk of developing cancers of the ovary, stomach, small bowel, pancreas, hepatobiliary, urinary tract, brain, and sebaceous neoplasms [77–80].

CRC in Lynch syndrome is the most common and first tumor, usually occurs between 41 and 54 years of age, compared to 69 years for sporadic CRC [28, 81]. Among first cancer detected in each patient the colorectal cancer cumulative incidences at 70 years by gene were 46%, 35%, 20%, and 10% for MLH1, MSH2, MSH6, and PMS2 mutation carriers, respectively [82].

Endometrial cancer (EC) is the most common extracolonic tumor in patient with Lynch syndrome and is the first malignancy in more than half of those women [78, 82, 83]. Risk for endometrial cancer appears to be particularly high for patients with MSH6 mutations [70, 74]. In addition to a 40–60% lifetime risk for endometrial cancer, women with LS have a 6–12% lifetime risk for ovarian cancer (OC) [83–85].

Overall, up to 15% of OCs are etiologically linked with hereditary susceptibility, of which 10–15% are attributable to mutations in MMR genes [84, 86, 87]. Ovarian carcinoma is the third most frequent malignancy in women with Lynch syndrome [82, 86]. Most frequent mutations are MSH2 (47%) and MLH1 (38%) [87]. Patients with LS often present with ovarian tumors at relatively younger age; unlike endometrial carcinoma in LS, most patients with ovarian cancer are younger than 50 years of age [85].

Neoplasms developing in patients with LS result from biallelic inactivation of the affected MMR gene when a second somatic alteration of the wild-type allele is acquired following the classical two-hit hypothesis [77, 78, 88]. MMR gene mutations lead to dysfunctional and structurally abnormal MMR proteins. This, in turn, results loss of MMR protein expression and tumor showing high-level microsatellite instability (MSI-H) [72, 89–91]. Tumors that show MSI-H or abnormalities in IHC for MMR proteins are called deficient MMR (dMMR) [76].

Microsatellite instability-high CRCs are more likely to be located in the colon proximal to the splenic flexure, often diagnosed at an early age (mean, 45–50 years) [1, 77, 91]. Although LS-associated endometrial cancers do not show

site-specific features such as LS-associated colorectal cancers, it has been suggested that as many as one-third of tumors arising in the lower uterine segment may be LS-related [92].

Morphologic features reported to be predictors of MMR deficiency in colorectal and endometrial carcinomas, including mucinous/signet-ring cell differentiation, medullary differentiation, tumor heterogeneity, and an expansive growth pattern. Tumor infiltrating lymphocytes (TILs) and peritumoral lymphocytes are often present in tumors with Lynch syndrome. Some peritumoral lymphocytes consist of nodular lymphoid aggregates that have been described as "Crohn-like" [71, 74, 84, 91, 93–95].

The phenotype of LS-associated endometrial and ovarian tumors is variable. The endometrial carcinomas can show a wide spectrum of histologic subtypes. Some studies reported that ECs were predominantly composed of endometrioid, well-differentiated, and FIGO stage I tumors [85, 92, 96]. Mills et al. show that the majority (80%, 32/40) of tumors with LS showed pure conventional endometrioid histology. Whereas some studies have described frequent aggressive morphologic features in tumors associated with MMR deficiency, namely higher grade, higher stage, and lymphovascular invasion, others have not. Some authors reported a higher frequency aggressive histologic subtypes, like serous, clear cell, undifferentiated, and dedifferentiated carcinomas [12, 97, 98]. A systematic reviews with LS-OCs revealed that the most frequently reported histological type was pure endometrioid carcinoma, mixed carcinoma (mucinous/endometrioid/clear cell carcinomas) or clear cell carcinoma [84, 87]. Most tumors (65%) were diagnosed at an early stage. The mean age at diagnosis was 45.3 (range 19–82) years [87]. Some authors conclude that LS-OC is characterized by tumor subtypes commonly associated with endometriosis, particularly endometrioid carcinoma [84].

Unfortunately, these histopathologic features are not specific or sensitive enough to be used alone for screening purposes or diagnostic for MSI [85, 88, 91, 94, 99].

MSI testing can either be performed via PCR or loss of MMR proteins, demonstrated by immunohistochemistry. The latter can be performed easily vith readly available MMR proteins for immunohistochemistry [28, 100, 101]. In LS, 90% CRC show high-frequency MSI (MSI-H) or abnormality in immunohistochemistry [76]. In Lynch syndrome-associated endometrial and ovarian carcinomas, mismatch repair was deficient in 97–100%, compared to 14–44% in sporadic cases [102]. Literature has demonstrated that the use of all four antibodies (MLH1, MSH2, MSH6, and PMS2) has a high sensitivity (ranging from 93% to 100%) for detecting high-level MSI and for predicting MMR gene mutation [78, 88, 91, 93].

Although MSI and MMR-IHC testing overall have a roughly 94% concordance rate in colorectal and endometrial cancer, MSI is particularly prone to missing MSH6 mutations, in up to half of MSH6-mutated cases [85, 103]. Tumors associated with MSH6 mutations are often MSI-low or microsatellite stable and because of MSH6 mutations are relatively more common in endometrial and ovarian cancers (compared with the GI tract), a larger proportion of cases may be missed if using only MSI testing for gynecologic cancers [92, 104]. However, dMMR is not specific for LS. Many tumors have deficiency in MMR proteins, but no germline mutations in genes encoding MMR proteins [88, 89, 103]. The majority of sporadic MSI colorectal carcinomas (loss of MLH1/PMS2 expression and high microsatellite instability) have MLH1 promoter hypermethylation, often, but not always, as a manifestation of CIMP [71, 74, 92, 101]. Two molecular genetic tests are currently used to identify these cases: MLH1 promoter methylation and BRAFV600E mutation testing. *BRAF* V600E somatic variant is observed in approximately 40% of sporadic MSI-H CRC cases but rarely in LS [71, 76, 91, 92, 101, 103]. Approximately 10–20% of endometrial carcinomas show loss of MLH1/PMS2 expression [78, 92]. Unlike colorectal cancer, BRAF mutations do not generally occur in association with sporadic methylation of MLH1 in endometrial

cancer. It is important to remember that the BRAF testing cannot be used for EC [76, 81, 92].

Patients with tumors without hypermethylation of the MLH1 promoter and absence of a detectable germline mutation in MMR gene or EPCAM and show anormal protein expression by immunohistochemistry (dMMR) are termed to have "Lynch-like syndrome" [93, 105]. Lynch-like syndrome is a heterogeneous condition [71, 76]. Conditions characterized by MMR deficient CRCs include Lynch syndrome (germline MMR mutation), Lynch-like syndrome (biallelic somatic MMR mutations), constitutional MMR deficiency syndrome (biallelic germline MMR mutations), and sporadic MSI CRC (somatic biallelic methylation of MLH1) [71]. Fifty to sixty percent of Lynch-like CRCs do exhibit the biallelic somatic inactivation of DNA MMR genes within the tumor [70, 71, 74, 89]. Distinguishing LS from these similar conditions is clinically important, since clinical management for patients differs according to the conditions [76, 88, 89].

Germline testing for mutations in the MMR genes is the gold standard for characterizing Lynch syndrome. Studies have found that germline mutations in most commonly MLH1 and MSH2 (60–80%), less frequently MSH6 (approximately 10%) and rare occasions PMS2 [70, 71, 74, 78, 106]. Specific mutations of DNA MMR genes are associated with differences in phenotype of Lynch patients. For instance, MLH1 and MSH2 mutation carriers present with cancers at younger ages (40–50 years), whereas MSH6 mutation carriers tend to be older at CRC diagnosis (age 50–65 years) with higher prevalence of endometrial cancer [71, 85]. Mutations in MSH6 and PMS2 genes have lower penetrance and different patterns of expression: MSH6 mutation carriers are thought to have a high risk of endometrial cancer, similar to that in MSH2 mutation carriers, but lower risks of CRC [82].

The guidelines are controversial concerning whether extended surgery such as total colectomy or total proctocolectomy for CRC should be proposed to people at risk [76, 107]. Prophylactic surgery, or hysterectomy with or without bilateral salpingo-oophorectomy or salpingectomy, has usually been advocated to women with having children is complete, or at the age of menopause. This procedure is cost-effective measure that significantly reduces the risk of gynecologic cancer in Lynch syndrome patients [76, 100, 108–111].

Prophylactic or risk-reducing hysterectomies and/or bilateral salphingoophorectomy (RRHBSO) may not show abnormalities on gross examination, and precursor lesions are frequently missed and grossly unrecognized. Histopathological examination of entire endometrium is recommended by investigators [84, 111–113]. Although a group investigator not recommend submitting unremarkable adnexal structures entirely for microscopic examination [96, 112], some authors and International Society of Gynecologic Pathologists have proposed the complete submission of the endometrium, ovaries, and fallopian tubes, for microscopic examination in RRHBSO for LS until larger experience is obtained [84, 111, 113].

In review of findings of prophylactic hysterectomy specimens in LS patients, endometrial findings have included most commonly hyperplasia, atypical hyperplasia, and small and low-grade endometrioid carcinoma [96, 114]. Endometrial hyperplasia has been reported up to 25% [112]. Incidental EC in LS patients has been described retrospective series prophylactic hysterectomies with a frequency between 5% and 17% [96, 108, 111, 112, 114]. Bartosch et al. [96] identified abnormal histological findings in 9/39 prophylactic hysterectomies: endometrial endometrioid carcinoma, atypical hyperplasia, and non-atypical hyperplasia [96]. Fedda et al. [111] found significant pathologic abnormalities in 17% of 29 patients with risk-reducing gynecologic surgery, all showing endometrial hyperplasia. None of their cases showed endometrial carcinoma and ovarian or fallopian tube malignancy [111]. Incidental EC in LS patients has been described retrospective series prophylactic hysterectomies with a frequency between 5% and 17% [111, 112]. In a study of 25 cases of RRHBSO in patients with LS, Karamurzin et al. [114] reported incidental EC or endometrial hyperplasia in 24% of case and OC in 4% [114].

Palma et al. reported one case of synchronous endometrial clear cell carcinoma and mixed endometrial and clear cell carcinoma of the fallopian tube [115].

There have been significant advances recently in diagnostic testing and the understanding of the molecular pathogenesis of Lynch tumors. Adenomatous polyps are thought to be the precursor lesion of CRC [101]. Although Lynch syndrome patients do not show an increase in the number of adenomatous polyps, hovewer, it is generally believed that neoplastic lesions in Lynch syndrome can transition from a benign adenoma to a cancer [81, 88, 101, 116]. There is some evidence to prove this. Dabir et al. show that in a meta-analysis, dMMR/MSI was present in 69.5% of conventional adenomas in LS patients, compared with 2.8% in unselected patients [90]. In their LS cohort, dMMR/MSI was more frequently present in patients older than 60 years. dMMR/MSI was also more common in villous adenomas (84%), adenomas over 1 cm (81%), and adenomas with high-grade dysplasia (88%). Ahadova et al. [117] found dMMR crypt foci adjacent to dMMR adenomas, suggesting a role for dMMR in adenoma initiation [117]. Similar to colorectal adenoma, some studies showed the loss of MMR protein immunoexpression in prophylactic hysterectomy with atypical and nonatypical hyperplasia [81, 96, 118].

Some authors have suggested that MMR misregulation is an early event both in endometrial and colon carcinogenesis and emphasized that MMR protein expression in precursor lesions, such as adenoma and endometrial hyperplasia, can be used as a screening tool for patients with suspected LS [81, 96].

Recent publications have demonstrated that histologically normal intestinal crypts in patients with Lynch syndrome can exhibit loss of MMR protein expression (MMR-deficient crypt) [83, 119, 120]. In the gastrointestinal tract, loss of MMR protein expression has been reported in 25–70% of nonneoplastic colonic and small bowel crypts, a subset of which also demonstrated MSI by PCR [83, 105, 118–121]. Wong et al. [105] showed MMR protein deficient nonneoplastic endometrial glands in all 19 cases the patients known germline mutation. None of the control cases of authors showed loss of MMR protein expression in nonneoplastic endometrium [105].

Advances in histopathology and sequencing, however, have led to other potential models of LS-associated colorectal carcinogenesis. Ahadova et al. have proposed a novel pathway for LS-associated colorectal neoplasia that completely bypasses adenomatous precursors altogether [117, 122]. Their data suggested some Lynch syndrome-associated colorectal cancers develop through an adenoma-independent, nonpolypous pathway of progression. Similarly, it was suggested that MMR-deficient nonneoplastic endometrial glands may represent the initial step in endometrial carcinogenesis in Lynch syndrome patients [82, 117, 122]. It was reported that MMR protein deficient colonic crypts or endometrial gland are a novel indicator of Lynch syndrome, and evaluation for MMR protein deficient crypts or nonneoplastic endometrium may be a helpful addition to Lynch syndrome diagnostics [105, 121].

Guidelines from several professional medical organizations and expert consensus groups advocate universal screening for LS in all newly diagnosed CRC and EC cases [70, 80, 88, 93, 109, 110, 121, 123]. Currently, the most common approach to universal screening for Lynch syndrome uses immunohistochemistry (IHC) to assess for absent expression of MMR proteins [88, 91, 93]. Algorithms may include MMR immunohistochemistry for MLH1, PMS2, MSH2, and MSH6 expression, and/or PCR testing for microsatellite instability (MSI) in tumoral tissue, followed by genetic counseling and germline genetic testing of selected patients [105]. Nowadays, dMMR CRC screening is thought to be useful not only as a diagnostic tool for LS, but also as a predictive, prognostic, and therapeutic marker [76, 81, 116].

26.6 Familial Adenomatous Polyposis Syndrome

Colorectal cancer is responsible for 8% of annual all deaths [124]. Two to five percent of all colorectal cancers are caused by hereditary syndromes [125]. Familial adenomatous polyposis syndrome (FAP) which is the second most common hereditary colorectal carcinoma is responsible for 1% of all colorectal carcinomas [126]. FAP is an autosomal dominant disease which is caused by a germline mutation of adenomatous polyposis coli (APC) gene. APC gene is located on chromosome 5q 21-q22 [127]. Due to mutation in APC gene Wnt signal pathway is disturbed and different mechanisms such as regulation of cell division, cell cycle, and extracellular adhesion are damaged and cause tumor formation [128].

More than 100 polyps are developed in colorectum due to mutation in APC gene. Due to the development of colorectal carcinoma during 35–40 years, it is necessary to perform proctocolectomy to these patients. Most of the tumors developed in these patients are located on left colon [129, 130]. According to guidelines, during macroscopic sampling of proctocolectomy specimens if there is a mass formation from polyps, polyp should be sampled totally. If the polyps do not have a malignant appearance, it is sufficient to sample them at about 10 cm intervals. The presence of colon mucosa in the surgical margins should be stated in the report, since polyposis and carcinoma development can be seen from these areas again [131, 132].

Adenomas and carcinomas which are seen in patients with FAP are histologically similar to spontaneous tubular adenomas and colorectal carcinomas. Crypts are lined by cells with hyperchromatic elongated nuclei. Although there is no maturation on cell surface, some adenomas may have focal villous protrusions. Some adenomas grow horizontally rather than polypoid. On the mucosa other than polyps, microscopic adenomas and dysplastic crypts (unicryptal adenomas) may be seen. Unicryptal adenomas are almost always pathognomonic for FAP [133].

There are other findings in these patients in addition to colonic polyps. Fundic gland polyps in stomach are seen in most of the individuals with FAP [134]. Also in duodenum and periampullary region adenomatous polyps are seen. In the patients with FAP duodenal and periampullary cancer is higher than normal population [135]. Also in this patients there is an increased risk of adenomas of small intestines and increased cancer risk from these adenomas. Small intestine and ampullary carcinoma incidence are found 4.5% in a study [136].

There are also extraintestinal findings in FAP. Fibroma, lipoma, epidermoid and sebaceous cysts, and nasopharyngeal angiofibromas may be seen [137]. Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is used for diagnosis of FAP patients. Bilateral CHRPE is specific for FAP [138]. Also, desmoid tumors can develop in the mesentery, abdominal wall or scar areas of individuals with FAP syndrome. Desmoid tumors are the third most common cause of death in individuals with FAP [139]. Other tumors which can be seen in this syndrome are mucinous pancreatic tumors, hepatoblastoma, and brain tumors [140, 141].

Turcot syndrome is one of the variants of the FAP. In this syndrome, in addition to gastrointestinal polyps, CNS tumors are found [142]. Most common CNS tumor seen in this patients is medulloblastoma [143]. Gardner's syndrome is another variant of FAP and in addition to gastrointestinal polyps fibromatosis, thyroid tumors, osteomas, dental anomalies, and lipomas may be seen in this variant [144, 145]. Attenuated adenomatous polyposis coli (AAPC) is milder form of the FAP and gastrointestinal adenomas are fewer in number (generally less than 50). Adenomas in this patients are generally located more proximally. Colorectal carcinoma development is less often in comparison to FAP and carcinoma development occurs at later ages [145].

Individuals with FAP have a 100% lifetime risk of developing colorectal carcinoma. After participating in an appropriate screening program this risk reduces immediately. When proctocolectomy is performed to this patients, ampullary and

duodenal cancer risk is impotant. Upper gastrointestinal tract of this patients should be examined regularly life long. Ampullary and duodenal cancers and desmoid tumors are the most important mortality causes of the patients who had decreased colorectal carcinoma risk by performing total colectomy [146].

26.7 Hereditary Breast and Ovarian Cancer Syndromes

26.7.1 Breast Cancer

Breast cancer is most common cancer among women worldwide [124]. Five to ten percent of breast cancers are caused by hereditary breast and ovarian cancer syndromes [147]. Mutations which cause hereditary breast and ovarian cancer syndromes are usually located in the BRCA1 and BRCA2 genes. Mutations in other genes and low penetrance alleles can be related to this syndrome [148]. At the age of 70, BRCA1 mutation carriers have a cumulative risk of breast cancer of 65% and ovarian cancer of 39%. Percentages for BRCA2 mutation carriers are 45% and 11%, respectively [149].

BRCA1 gene is a tumor supressor gene which is located on chromosome 17q21 [150]. BRCA1 is a pleiotropic DNA damage response protein which is responsible for control point activation and DNA repair [151]. Breast tumors seen in BRCA1 mutation carriers are generally high-grade intraductal and infiltrative ductal carcinomas [152]. But this tumor have different properties than sporadic breast carcinomas. BRCA1-mutated tumors have high mitotic activity, pushing borders, and prominent lymphocytic infiltration [153]. Also, this tumors are negative for estrogen receptor, progesteron receptor, and HER2 [154].

BRCA2 gene is a tumor supressor gene which is located on chromosome 13q12-13 [155]. BRCA2 is a mediator located in the main mechanism of homologous recombination [151]. Most common tumor type seen in BRCA2-mutated patients is invasive ductal carcinoma. These tumors have less tubule formation, higher mitotic activity and prominent nuclear pleomorphism, pushing borders, and prominent lymphocytic infiltration [156, 157]. BRCA2-mutated tumors have similar ratios to sporadic tumors about estrogen and progesteron receptor positivity but they are generally HER2 negative. BRCA2-mutated tumors are also more likely to present with isolated ductal carcinoma in situ and microcalcifications that can be detected using screening mammography [154–157].

Bilateral prophylactic mastectomy should be performed for reducing the risk of breast cancer in BRCA1 and 2 carriers [158]. Bilateral prophylactic mastectomy reduces the relative risk as 90–100% in BRCA1 and 2 carriers who were not diagnosed as breast cancer before [159]. Efficacy of the bilateral prophylactic mastectomy is affected by the factors like surgery method and whether the patient had bilateral oophorectomy or not. In patients who had bilateral prophylacticoophorectomy only, reduction in breast cancer risk is 47–68% [155, 160, 161]. In BRCA mutation carriers after breast conserving surgery, ipsilateral carcinoma recurrence is 49% during the 12 years follow-up period [162].

In studies where prophylactic mastectomies were examined histopathologically, it was stated that there is not a standard macroscopic sampling method for resection materials, different institutions have different applications. In a study, X-ray was performed for specimen and suspicious areas in X-ray, macroscopic examination, and also nipple is sampled [163]. In another study, two samples were taken from every quadrant and nipple were sampled and in addition to this macroscopically suspicious areas were sampled [164]. In a study with a higher rate of occult cancer specimens were cooled and sliced approximately 5 mm intervals and radiography had done to the slices [165]. In addition to suspicious lesions, random areas from each quadrant and nipple were sampled. Occult cancer detection rate is 0.5–11.3% in prophylactic mastectomy materials [166, 167]. Histopathological types of occult cancers detected in prophylactic mastectomy specimens were invasive ductal carcinoma, invasive lobular carcinoma, and micro- invasive lobular carcinoma

[164, 168]. Other than occult cancers there were high risk lesions like ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), atypical ductal hyperplasia (ADH), and atypical lobular hyperplasia (ALH) in prophylactic mastectomy materials. In BRCA mutation carriers, frequency of lesions with high risk of developing invasive carcinoma like ADH, ALH, and LCIS is higher than normal population [169].

Sentinel lymph node biopsy (SLNB) is a standard procedure for patients with early-stage breast cancer who have clinically negative lymph nodes [170]. Although there are studies about whether sentinel lymph node biopsy (SLNB) should be performed routinely in patients undergoing prophylactic mastectomy, there is no consensus and no information in guidelines about this procedure. Despite the morbidity of the SLNB is much lower than the axillary lymph node dissection, SLNB has complications such as axillary paresthesia, motion restriction and lymphedema in upper extremity, axillary seroma, and hematoma [171–173]. In the studies which prophylactic mastectomy and SLNB were performed, positive sentinel lymph node ratios were 0–3.5% [172–179]. In patients who had prophylactic mastectomy and SLNB, most common pattern of lymph node involvement is micrometastasis or immunohistochemically positive individual tumor cells [164]. But prognostic significance of the micrometastasis or isolated tumor cells is not known [180]. In a meta-analysis, 2.8% of the patients who had undergone prophylactic mastectomy and SLNB had benefitted from the procedure [181]. When benefit ratios and complications were evaluated, SLNB is not effective during every prophylactic mastectomy procedure and to every patient.

Different studies had done about the relationship between BRCA1 and BRCA2 mutation and breast carcinoma prognosis. In some studies, there was no difference in disease-free and overall survival rate between the BRCA1 related and sporadic carcinomas [182, 183]. In another study which had done by different analysis method, Ashkenazi Jewish patients who were BRCA1 mutation carriers had statistically poor prognosis than Ashkenazi Jewish patients who were not mutation carriers [184].

26.7.2 Ovarian Cancer

Ovarian and fallopian tube cancers account for 2.5% of cancers in women [185]. Germline mutations in BRCA gene are responsible for 4–11% of these tumors [186]. At the age of 80, ovarian cancer risk of BRCA1 and BRCA2 carriers is 44% and 17%, respectively [187]. Efficacy of bilateral salphingoophorectomy (BSO) for reducing the ovarian cancer frequency was shown [188]. BSO reduces gynecological cancer risk 85–95% in BRCA mutation carriers [189]. Also, in the studies premenopausal BSO reduces the breast cancer risk in high risk patients [190]. The National Comprehensive Cancer Network (NCCN) and Society of Gynecologic Oncology (SGO) guidelines suggest risk-reducing salphingoophorectomy to the BRCA mutation carriers after childbirth request is completed and before 40 years old [191].

Overall, ovarian carcinomas harboring BRCA1/2 mutations are far more likely to exhibit high-grade serous carcinoma (HGSC) histology. BRCA1/2 deficient tumors tend to be associated with higher grade, poor differentiation, higher mitotic index, severe nuclear atypia, and tumor infiltrating lymphocytes [192, 193].

In histopathological examination of the bilateral salphinoophorectomy materials occult malignancy rates were 5.4–9.1%. Some of the occult tumors were located in ovary, some of them were located in fallopian tube, and some were located in both. High-grade serous carcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, and serous papillary carcinoma were the histopathological types of the tumors seen in this specimens [193–195]. The occult carcinomas with typical morphology of high-grade serous carcinoma despite their small size, have a significant risk of recurrence. Serous tubal intraepithelial carcinoma (STIC) which is thought to be a precancerous lesion of the tubal and ovarian malignancies was seen in the 1–12% of the specimens and generally located in the fimbrial end [192–201]. STIC is a localized lesion showing minimal epithelial tufting/stratification, loss of nuclear polarity, nuclear enlargement, hyperchromasia, irregular chromatin pattern, nucleolar promi-

nence, apoptosis, and mitoses. The morphological findings must be supported by abnormal p53 staining and increased proliferation index with at least 10% of lesional nuclei expressing Ki-67 to confirm this diagnosis [192–196].

In a meta-analysis, overall survival and progression-free survival of ovarian cancer were shown to be better in patients with BRCA1 and BRCA2 mutation carriers, regardless of tumor stage, grade, or histological subtype than patients who were not carriers [202].

26.8 Conclusion

The identification of pathognomonic morphologic and immunohistochemical clues is crucial to raise the possibility of an inherited genetic disorder and to guide further management, including gene testing, counseling, and targeted therapy. In these familial cancer syndromes, due to the complex medical, ethical, social, and psychological aspects of these diseases management should be performed by a multidisciplinary team consisting of a surgeon, medical oncologist, geneticist, and pathologist with support from multiple other specialties.

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Prophylactic Surgery for Genetic Predisposition of Female Organs

27

Nuri Yildirim, Duygu Guzel, and Ali Akdemir

27.1 Introduction

Currently, rapid developments in molecular biology techniques allow the identification of mutations and the inherited diseases with which they are associated. Determination of risk groups for germline mutations is possible with genetic counseling. Thus, before the disease occurs, it can be decided which patient population will be screened and whether they are candidates for risk-reducing prophylactic treatment.

The most common clinical-related hereditary syndromes in gynecological oncology are hereditary breast ovarian cancer syndrome due to BRCA 1/2 mutation [1]. After the identification of BRCA 1 and 2 genes in 1994 and 1995, respectively [2], many patients have had the opportunity of early diagnosis and preventive treatment for breast and ovarian cancer with the detection of mutations in these genes. With the identification of other hereditary syndromes such as Lynch (MLH1, MSH2, MSH6, PMS2), Li–Fraumeni (TP53), Cowden (PTEN), and Peutz–Jeghers syndromes (STK11), effective screening and prophylactic surgery recommendations for gynecological cancers with genetic predisposition have been published by various guidelines.

There are many prophylactic surgery options described in the literature. Effective screening programs, prophylactic risk reduction surgery, and its timing are discussed in this chapter in the light of the literature.

27.2 Hereditary Breast and Ovarian Cancer

The majority of hereditary breast and ovarian cancers are caused by mutation of BRCA1 and BRCA2 tumor suppressor genes that are inherited autosomal dominantly [3] and located on chromosomes 17q21 and 13q12-13, respectively [4]. Women who are carriers of the BRCA 1/2 mutations have an increased risk of developing breast and ovarian cancer. At least 5–10% of all ovarian cancers were found to be associated with BRCA mutations [5]. The overall prevalence of BRCA1/2 mutations has been estimated from 1:300 to 1:500 [6]. While 81% of the hereditary breast and ovarian cancer cases occur due to BRCA1 and 14% due to BRCA2 mutation, BRCA2 is responsible for 76% of all familial breast cancers [7]. In the meta-analysis of 22 studies, the average cumulative risks in BRCA1 and BRCA2 carriers by age of 70 were calculated as 65% and 45% for breast cancer and 39% and

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11% for ovarian cancer, respectively [8]. BRCA mutation carriers have also been shown to have an increased risk for male breast cancer, melanoma, pancreatic, prostate, colon, fallopian tube and primary peritoneal carcinoma [9–13]. The incidence of BRCA 1/2 mutations differs in various ethnic groups and populations. Ashkenazi Jews, Icelanders, Norwegians, Finns, French, Swedes, Dutch, Italians, Pakistanis, South Africans, Hispanics, French-Canadians, and Afro-Americans are known to have founder mutations [14]. In Ashkenazi Jews, 1 in 40 individuals carry one of the three founder mutations of BRCA 1 or 2 [6].

High grade serous carcinoma (HGSC) is the most frequently reported histological type (76.7–93%) in women with hereditary breast ovarian cancer syndrome [15]. The risk for HGSC is less than 2% in the general population, up to 40% in BRCA1 carriers and up to 25% in BRCA2 carriers [16]. Studies have found that mucinous carcinomas and ovarian tumors with low malignancy potential are not associated with the BRCA1/2 mutation [17]. Ovarian cancer patients with BRCA mutations have higher sensitivity to platinum and poly (ADP ribose) polymerase (PARP) inhibitors [18, 19]. Patients with ovarian cancer, who are BRCA1 carriers, have a longer survival and better chemotherapy response [20].

Breast cancers developed because of the BRCA1 mutation are more aggressive and higher grade compared to BRCA2 due to the hormone receptor status. Approximately 78% of patients with BRCA1 mutation are triple negative (hormone epidermal growth factor receptor 2 (HER-2), estrogen receptors (ER), and progesterone receptors (PR)) with worse prognosis [21].

27.2.1 Management

Identification of BRCA1/2 carriers helps to provide appropriate genetic counseling to the patient and family, and to plan alternative treatment or prophylactic risk-reducing surgery options according to the fertility expectation of the patient. Women who need genetic counseling and testing for BRCA1/2 due to the risk of having a predisposition to hereditary breast, ovarian, tubal, and peritoneal cancer are as follows [22]:

- Individuals with relatives who have a known pathogenic or possibly pathogenic variant in the cancer susceptibility gene.
- Individuals who meet the following criteria but previously used limited testing and want multi-gene testing.
- Diagnosed at ≤45 years for breast cancer.
- Breast cancer diagnosed between 46 and 50 years of age with limited or unknown family history, or a second breast cancer diagnosed at any age, or diagnosed for ovarian carcinoma/fallopian tube/primary peritoneal carcinoma, metastatic prostate cancer, pancreatic cancer at any age, in at least 1 close relatives.
- Triple-negative breast cancer diagnosed at ≤60 years.
- Ashkenazi Jews diagnosed with breast cancer at any age.
- Ovarian, pancreatic, or metastatic prostate cancer at any age, or breast cancer diagnosed at <50 years.
- At any age, in at least 1 close relatives; diagnosed for ovarian carcinoma/fallopian tube/primary peritoneal carcinoma, metastatic prostate cancer, pancreatic cancer.
- ≥3 total diagnoses of breast cancer in patient and/or close relative.
- Diagnosed of male breast cancer in a close relative at any age.
- For all patients with a history of ovarian carcinoma, pancreas, metastatic prostate, and male breast cancer at any ages.
- Patients of any age with a history of high grade prostate carcinoma (Gleason score ≥ 7) with any of the following: a history of ovarian, pancreatic or metastatic prostate cancer at any age in at least one relative or breast cancer diagnosed at <50 years, two relatives diagnosed with breast or prostate cancer at any age or Ashkenazi Jewish ancestry.
  - Close relative is defined as a first-, second-, or third-degree blood relatives on the same

side of the family (either maternal or paternal side).
– Limited family history includes fewer than 2 first- or second-degree female relatives surviving beyond 45 years on either the maternal or paternal side.

27.2.2 Screening

The recommendations of the expert groups for breast cancer screening in the National Comprehensive Cancer Network (NCCN), the American College of Obstetricians and Gynecologists (ACOG), and the European Society for Medical Oncology (ESMO) are as follows [22–24].

27.2.2.1 Breast Cancer

Breast awareness training should be given to women who are BRCA1/2 carriers from the age of 18. All mutation carriers should be warned to seek immediate medical attention if they detect any changes in their breasts or axilla with regular breast examination (BSE). BSE is recommended to be performed especially at the end of the menses in women in the premenopausal period. A clinical breast examination should be started every 6 months from the age of 25. Women should be screened with an annual contrasted breast MRI (magnetic resonance imaging) or annual mammography (only if MRI is not available) between the ages of 25–29. Screening can be individualized if the family history includes breast diagnosis before 30 years of age. Although MRI is more sensitive than mammography for detection of breast cancer [1], the combined use of MRI, clinical breast examination, and mammography has the highest sensitivity. Both contrasted breast MRI and mammography are evaluated together between 30 and 75 years of age. Patients over 75 years old should be evaluated individually. For women with BRCA1/2 mutations who are treated for breast cancer and have not had bilateral mastectomy, annual mammography screening is recommended considering tomosynthesis and breast MRI.

27.2.2.2 Ovarian Cancer

For patients who have not elected to undergo risk-reducing salpingo-oophorectomy or who are postponing the procedure, a proven benefit of the combined use of transvaginal ultrasound and serum CA-125 level starting at the age of 30–35 years has not been demonstrated and may be considered in a limited patient at the discretion of the clinician. There is still no effective surveillance method for ovarian cancer [25].

27.2.3 Risk-Reducing Surgical Procedures

The patient should be included in the screening program as soon as the mutation is detected; intensive surveillance, chemoprevention, or risk-reducing prophylactic surgery for ovarian and breast should be discussed. Prophylactic risk-reducing surgical procedures significantly reduce the risk of developing cancer but cannot eliminate it completely. The treatment options and their timing should be individualized to the patient.

27.2.3.1 Breast Cancer

Bilateral prophylactic mastectomy is the most effective risk-reducing method in BRCA carriers [26]; studies show that this procedure decreases the incidence of breast cancer by 90% or more [23, 27]. Various surgical options are available, such as total mastectomy, skin-sparing mastectomy (SSM), and nipple-sparing mastectomy (NSM) [23]. Sentinel lymph node biopsy is not indicated because of the probability of detecting an occult breast cancer less than 5% at the time of surgery [23]. In one study, nipple-sparing mastectomy performed on 346 women with BRCA1/2 carrier was found to be highly protective against breast cancer. No patient developed breast cancer in routine follow-up [28]. In women with BRCA1/2 carriers once diagnosed with breast cancer, the risk of developing cancer in the opposite breast has been shown to be 16–55% in 25 years [29]. Although contralateral prophylactic mastectomy has been shown to reduce this

risk by about 95%, in the other breast, no survival benefit has been demonstrated yet by prospective randomized studies [30].

In studies that evaluate patient satisfaction after prophylactic mastectomy, while negative effects on quality of life were not found, undesirable results were reported in terms of sexuality and body image perception [31]. It is the preferred approach to offer breast reconstruction to the patient immediately after mastectomy [26]. Multidisciplinary counseling service should be provided to the patient, and long- and short-term complications and psychological effects should be explained in detail [24].

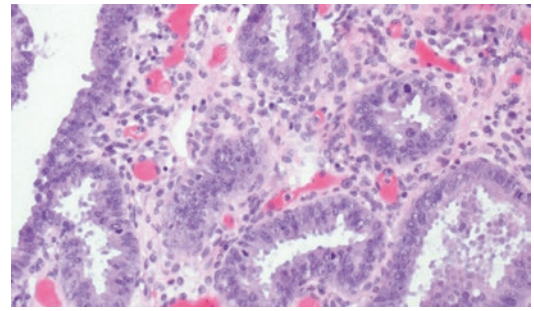

Fig. 27.1 Serous tubal intraepithelial carcinoma (STIC) with irregular luminal surface, epithelial stratification, and nuclear atypia in the fallopian tube epithelium (H&E, 200×)

27.2.3.2 Ovarian Cancer

The most effective primary prevention in BRCA1/2 carriers is bilateral salpingo-oophorectomy, which reduces the risk of ovarian cancer by 80–90% and breast cancer by 40–50%, and has also been shown to reduce overall mortality [23, 32–34]. The incidence of occult ovarian cancer in BRCA1 carriers was 1.5% before the age of 40, and 3.8% between the ages of 40 and 49; in BRCA2 carriers, only 1% was reported before the age of 50 [23]. NCCN guideline recommends risk-reducing salpingo-oophorectomy (RRSO) for all BRCA1 carriers between the ages of 35 and 40. For BRCA2 carriers, since the age of onset is usually later, RRSO can be delayed until the age of 40–45, unless the age of diagnosis in the family requires an earlier time for this operation. This suggestion should be considered only after childbearing is completed [22]. Hysterectomy is not routinely recommended [35].

At the beginning of the operation, all organ and peritoneum surfaces should be carefully evaluated for the presence of tumoral implants and pelvic washing fluid should be taken [24, 36]. A biopsy should be taken from suspicious areas. *Infundibulopelvic ligament* should be ligated 2 cm proximal to the ovary. Ovaries and fallopian tubes should be completely removed [24, 37]. And then, they should be scanned with microscopic serial sections for occult tumors [24]. Occult malignancies were found in 2–10% of patients who underwent prophylactic risk-reducing surgery [38]. The majority of this tumors have been shown to be located in the fallopian tube [39]. In BRCA mutation carriers, the incidence of serous tubal intraepithelial carcinoma (STIC) has been shown to be 0.6–7% (Figs. 27.1 and 27.2) [40]. Women with BRCA1/2 mutation have less than 5% risk of developing primary peritoneal carcinoma after RRSO [41, 42]. If hysterectomy will not be performed, the fallopian tube should be divided from its junction with the uterus corn. When the operation is performed laparoscopically, specimens should be taken out of the abdomen with endoscopic bag. Routine intraoperative frozen section procedure is not recommended [24]. It is not clear which surgical technique (e.g., laparotomy versus laparoscopy) should be chosen [20, 43]. Minimally invasive surgery has been shown to be an effective and safe option in BRCA carriers [38].

Women with the BRCA1 mutation have an increased risk for ovarian and breast cancer as well as serous endometrium cancer so concurrent hysterectomy option should be considered in women with BRCA1 mutation [44]. In a study carried out, in 40-year-old women who are BRCA1 carrier, the addition of a hysterectomy to the risk-reducing salpingo-oophorectomy was shown to be cost-effective and associated with a mean additional 4.9-month survival [45]. The Cochrane review, which included 10 cohort studies with participants carrying the BRCA1/2 mutation, showed that overall survival was longer in patients undergoing RRSO compared to those without RRSO [46].

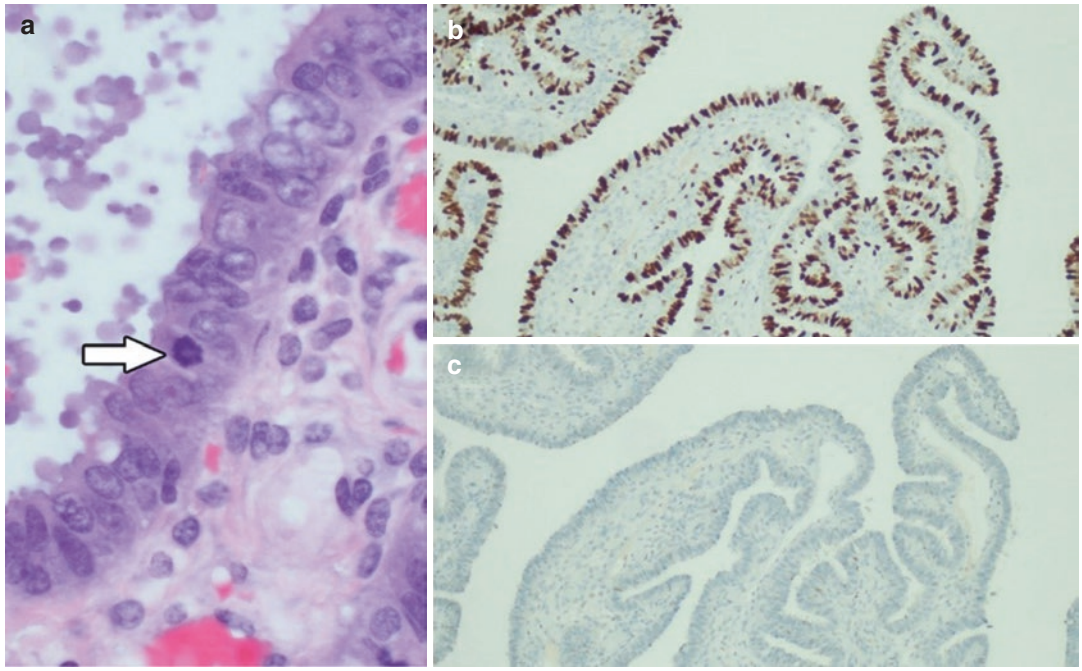

Fig. 27.2 (**a**) In serous tubal intraepithelial carcinoma (STIC), the atypical mitosis cell between the cells with nuclear pleomorphism is marked by an arrow (H&E, 600×). (**b**) High Ki67 proliferation index in immune staining in STIC. (**c**) Complete loss of nuclear p53 expression in serous tubal intraepithelial carcinoma (null pattern)

The results of risk-reducing surgical procedures in women with BRCA mutation carriers indicated the presence of early tubal malignancy in 1–5% of patients. Supporting retrograde menstruation theory, tubal ligation has been shown to be protective against endometrioid and clear cell ovarian carcinomas [47]. In BRCA carriers, prophylactic salpingectomy and delayed oophorectomy (PSDO) can be considered as an alternative to RRSO against early menopausal risks [39]. In a study comparing RRSO and bilateral salpingectomy in women with BRCA mutations, BSO was shown to be the most effective risk-reducing procedure and was associated with the highest life expectancy and lowest cost [48].

Patients in the premenopausal period may experience acute surgical menopausal symptoms after RRSO, which causes a decrease in quality of life (QoL) such as hot flashes, night sweats, sleep disturbances, cognitive changes, vaginal dryness, and loss of sexual interest [49, 50]. However, some studies have shown that RRSO has no negative effect on quality of life (QoL) in high-risk women [51, 52]. Nevertheless, symptoms that decrease sexual satisfaction after prophylactic surgery and lead to a decrease in sexual functions have been reported more frequently [52]. RRSO has been shown to be associated with some long-term adverse effects such as changes in lipid profile, coronary heart disease, and osteoporosis, as it reduces the age of onset of menopause [20].

Several studies have reported that short-term use of HRT is safe in alleviating symptoms that develop after surgical menopause. Regardless of the hormone receptor status, HRT is not recommended in patients previously diagnosed with breast cancer [23].

In the postoperative follow-up, the patient should be evaluated twice a year with transvaginal ultrasound and CA125 levels [27].

27.2.3.3 Chemoprevention

The use of tamoxifen, which inhibits the action of estrogen on breast tissue, has been shown to increase disease-free survival and reduce the risk

of contralateral breast cancer in patients with estrogen receptor positive breast cancer [53]. Chemoprevention with tamoxifen is associated with increased endometrial cancer, thromboembolic events, cataracts, and menopausal symptoms [54]. Studies have shown that the use of oral contraceptives (OKS) reduces the risk of ovarian cancer in BRCA1/2 carriers [55, 56].

27.3 Lynch Syndrome

Lynch syndrome (LS) or hereditary nonpolyposis colorectal cancer (HNPCC) is a genetic syndrome defined by Lynch in 1966, inherited as an autosomal dominant and responsible for 3–5% of colorectal cancers [57, 58]. Lynch syndrome, which constitutes 10–15% of hereditary ovarian cancers [59], is characterized by the presence of a mutation in one of four DNA mismatch repair (MMR) genes such as MLH1, MSH2, MSH6, and PMS2 [58, 60]. The expression loss of MSH2 has also been associated with mutations in EPCAM [60]. Unlike hereditary breast ovarian cancer syndrome, genetic assessment in Lynch syndrome can be performed by immunohistochemically evaluating the tumor for mismatch repair proteins [61]. Studies show that LS causes predisposition not only for colorectal carcinomas, but also for endometrium, ovary, stomach, small intestine, hepatobiliary tract, pancreas, renal pelvis, ureter, breast, brain (glioblastoma) and prostate cancers [59]. The lifetime risk in women with LS is 40–60% for endometrium and colon cancer, while it is 9–12% for ovarian cancer [61]. Endometrial and ovarian cancers associated with Lynch syndrome are usually diagnosed at an earlier age than the general population. The mean age of diagnosis for both cancers is in the fifth to sixth decade of life [57]. The most common histological subtype of endometrial cancer is the endometrioid type, but the presence of others (such as clear cell, papillary serous, and MMMT) has been demonstrated. The risk of lower uterine segment involvement is higher [62].

27.3.1 Management

Surveillance, detailed screening, chemoprevention, and risk reduction surgery are available for women with Lynch syndrome to prevent or detect endometrium and ovarian cancer early [63]. Genetic evaluation recommended by Society of Gynecologic Oncology (SGO) for increased risk of Lynch syndrome [61]:

- Patients with endometrium or colorectal cancer with loss of a DNA mismatch repair protein or microsatellite instability (MSI) in immunohistochemistry.
- Patients whose first-degree relatives were affected by endometrium or colon cancer, either diagnosed before the age of 60, or found to be at risk for Lynch syndrome by systematic clinical screening.
- Patients with known mismatch repair gene mutations in their first- or second-degree relatives.

The current NCCN guideline recommendations for Lynch syndrome are as follows [64]:

Endometrium cancer: Since early detection of endometrial cancer is often possible based on symptoms, women should be made aware of the importance of any abnormal uterine bleeding or postmenopausal bleeding. These symptoms must be evaluated with an endometrial biopsy.

Although prophylactic hysterectomy does not decrease mortality in endometrial cancer, it can reduce the incidence of cancer. Therefore, hysterectomy can be considered as a risk-reducing procedure. The timing of hysterectomy can be individualized according to conditions such as the completion of childbearing, comorbidities, the pathogenetic variant of the LS gene, and family history.

The benefit of endometrial cancer screening in women with Lynch syndrome has not been demonstrated. However, since endometrial biopsy is highly sensitive and specific in diagnosis, screening with an endometrial biopsy may be considered every 1–2 years.

The benefit of screening with transvaginal ultrasonography has not been demonstrated in postmenopausal women. It can be considered at the clinician's discretion. It is not recommended in women in the premenopausal period due to the changes in endometrial thickness.

Ovarian cancer: Bilateral salpingo-oophorectomy (BSO) can be considered a risk-reducing procedure in women who have completed childbearing because of the potential to reduce the incidence of ovarian cancer. The timing of BSO can be customized according to conditions such as completion of childbearing, comorbidities, pathogenetic variant of the LS gene, and family history. There is insufficient evidence to perform risk-reducing salpingo-oophorectomy (RRSO) in those with MSH6 and PMS2 pathological variants.

Since there is no effective screening for ovarian cancer, patients should be informed about possible symptoms such as abdominopelvic pain, bloating, weight loss, and early satiety.

Routine ovarian cancer screening is not supported in patients with LS. Transvaginal ultrasonography and serum CA125 levels are not sensitive or specific enough for ovarian cancer; their use may be considered according to the doctor's discretion.

European Society for Medical Oncology (ESMO) and the American College of Gastroenterology (ACG) guidelines recommend all women with LS follow-up with an annual transvaginal ultrasound and endometrial biopsy from the age of 30–35. Hysterectomy and bilateral salpingo-oophorectomy should be offered to women between the ages of 40–45 who have completed childbearing [23, 65]. A study by Schmeler et al. revealed that prophylactic total hysterectomy and bilateral salpingo-oophorectomy is an effective method of preventing endometrium and ovarian cancer in women with LS [66]. It should be remembered that patients undergoing prophylactic surgery have a risk of occult malignancy [60]. Cases of primary peritoneal carcinoma have been reported after oophorectomy for Lynch syndrome [63].

There is no consensus yet for endometrium and ovarian cancer surveillance and screening in women with Lynch syndrome. The sensitivity of transvaginal ultrasonography in screening for endometrial cancer has been shown to be low [62].

Several studies have shown that the use of oral contraceptives in high-risk women with Lynch syndrome can provide an effective chemoprevention for ovarian and endometrial cancer [62]. The risks associated with HRT use in women with LS have been shown to be lower compared to patients with BRCA mutations [58].

27.4 Peutz–Jeghers Syndrome

Peutz–Jeghers syndrome (PJS) is a rare disease characterized by mutation in the STK11 (LKB1) gene, with an autosomal dominant inheritance, clinically susceptible to gastrointestinal hamartomatous polyps, mucocutaneous pigmentation, and susceptibility to various malignancies [67]. The presence of two of the three criteria is diagnostic for PJS: mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers; family history for PJS; and presence of 2 or more hamartomatous polyp in the gastrointestinal tract [59, 63]. The average age of diagnosis for PJS has been reported to be 26 years in women [68]. The lifetime risk of cancer in PJS was 32–54% for the breast, 18–21% for the ovary, 10% for the cervix, and 9% for the uterus, respectively [64]. Sex cord tumors with annular tubules (SCTATs) associated with PJS typically occur in young adults with signs of menstrual irregularity and hyperestrogenism. Unlike sporadic cases, they are usually bilateral and microscopic [67].

27.4.1 Management

Patients should be screened for breast cancer from the age of 25, with annual mammography and breast MRI, and a clinical breast examination every 6 months. For the screening of gynecological malignancies, it is sufficient to perform an annual pelvic examination and pap smear from the age of 18–20 [64].

ESMO guidelines recommend clinical breast examination every 6–12 months starting from

20–25 years old, annual breast MRI between 20 and 29 years old, annual mammography and/or MRI between 30 and 75 years old, and annual gynecological follow-up. In addition, risk-reducing mastectomy should be considered [23].

27.5 Li–Fraumeni Syndrome

Li–Fraumeni syndrome (LFS) is an autosomal dominant inherited disease caused by the germline mutation of the TP53 gene located on chromosome 17p13.1. Because the TP53 gene mutation causes loss of function in P53, patients face many early-onset risks of malignancy [69]. LFS has been associated with many malignancies: brain tumors, adrenocortical carcinoma, soft tissue sarcomas and bone tumors, hematologic malignancies, breast cancer (generally very early in onset), lung, skin, gastrointestinal tract, kidney, thyroid and neuroblastoma [70]. Approximately 50% of TP53 mutation carriers have a risk of developing cancer by age 30. While the lifetime risk is 70% for men, it is almost 100% for women [71]. Breast cancer accounts for about 25–30% of LFS-related tumors. Unlike hereditary breast cancers associated with the BRCA mutation, it affects only women with LFS [72]. Cumulative incidence rate for breast cancer by age 70 years was reported as 54% among women [73]. Patients with LFS are at risk for second malignancies arising from the radiation field [74].

27.5.1 Management

According to current NCCN guideline recommendations [22], the patient should be made conscious in terms of breast awareness from the age of 18. Clinical breast examination should be done every 6–12 months from the age of 20. Breast should be screened with an annual contrast breast MRI between the ages of 20–29 and an annual contrast breast MRI and mammography between the ages of 30–75. If over 75 years old, screening can be individualized. Patients diagnosed with breast cancer who do not have bilateral mastectomy and are carriers of the TP53 variant are recommended with annual breast MRI and mammography. Considering genetic counseling, reconstruction options, degree of protection, and possible risks, the risk-reducing mastectomy option should be discussed in detail. Psychosocial aspects and its effect on quality of life should be shared with the patient.

ESMO recommends avoiding ionizing radiation (e.g., CT), risk-reducing mastectomy, and PGD options before pregnancy to patients with Li–Fraumeni syndrome [23].

27.6 Cowden Syndrome

Cowden syndrome (CS), which is inherited as an autosomal dominant and occurred due to germline disorders in the PTEN (The phosphatase and tensin homolog) tumor suppressor gene located on chromosome 10, is a rare disease characterized by multiple hamartomatous lesions [75, 76]. Women with Cowden syndrome have an increased risk for malignancies such as breast, thyroid, bladder, ovarian, endometrium and cervical cancer [77, 78]. The most common accompanying malignancy is breast cancer. Lifetime cancer risk has been shown to be 25–50% [77].

27.6.1 Management

According to the NCCN guideline recommendations [22], women with CS should be trained about breast awareness from the age of 18. Clinical breast examination, every 6–12 months should be recommended starting at age 25 years or 5–10 years before the earliest known breast cancer in the family. Breast screening should be performed with mammography and breast MRI starting from the age of 35 or 5–10 years before the earliest known breast cancer in the family. After 75 years of age, patients should be evaluated individually. It is recommended that PTEN pathological and possible pathological variant carriers that are treated for breast cancer but have not had a bilateral mastectomy should be screened with annual mammography and breast MRI. Risk-reducing mastectomy should be discussed.

For endometrial cancer, screening should be started by the age of 35. Patients should be advised to keep a calendar to detect menstrual cycle irregularities. Also, they should be informed of symptoms such as abnormal uterine bleeding and postmenopausal bleeding. If these findings are present, patient should be evaluated by endometrial biopsy. Although endometrial cancer screening has no proven benefit in women with CS, screening with an endometrial biopsy may be considered every 1–2 years due to the high sensitivity and specificity. The benefit of transvaginal ultrasound in screening in patients in the premenopausal period has not been demonstrated. It can be used in the postmenopausal period at the discretion of the doctor.

ESMO guideline recommends that the patient be offered risk-reducing mastectomy, risk-reducing hysterectomy, and PGD before possible pregnancy [23].

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Prophylactic Surgery for Benign Gynecologic Pathologies

28

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28.1 Introduction

The first goal of the prophylactic surgery is to lower the risk of cancer. The procedures to prevent any disease or undesirable consequences are very essential, especially in prophylactic surgery for benign gynecologic pathologies. Prophylactic salpingectomy, anti-prolapses surgery, and prophylactic cerclage can count in procedures related to prophylactic surgery for general gynecology.

Prophylactic salpingectomy is the removal of bilateral salpinx during pelvic surgery which is performed for another indication. Its primary aim is to reduce the risk of ovarian cancer which has very poor prognosis. Prophylactic salpingectomy can be performed to female sterilization, infertility surgery, and after hysterectomies. These procedures do not increase the risk of surgery, and cost-effective approach considering possible adnexal surgery costs in the future when tubes left in place.

Pelvic organ prolapses have significantly negative effects on quality of life. Treatment of pelvic organ prolapse is not hysterectomy. Conversely, hysterectomy may cause the problems getting worse. McCall culdoplasty and uterosacral ligament suspension as apical suspension procedures are safe and effective procedures for women who candidates to prophylactic prolapses surgery after hysterectomy.

Prevention of preterm delivery is one of the major issues in modern obstetrics, and cervical insufficiency is one of the many reasons of preterm delivery. Prophylactic cerclage is a procedure performed based on history of cervical insufficiency with high take home baby ratio.

Prophylactic appendectomy is removing appendix at unrelated surgical procedure. Prophylactic appendectomy reduces pain significantly in patient with chronic pelvic pain. Furthermore, women who will have pelvic or abdominal radiation or chemotherapy, patients who will have major operations in which dense adhesions are anticipated after procedure, and disabled patients who will have difficulty for describing possible appendicitis symptoms also benefit from prophylactic appendectomy.

If there is a chance for prophylactic procedure before planned pelvic surgery, patient should be fully informed and written consent should be obtained with any decision before surgery.

28.2 Prophylactic Salpingectomy

Prophylactic salpingectomy is the excision of the bilateral salpinx in order to prevent potential fallopian tube, ovary and peritoneum carcinoma

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when any other pelvic surgery performed for another indication in women [1].

28.2.1 Background and Benefits

Ovarian cancer is typically diagnosed in advanced stage and accordingly has poor prognosis. Limited screening and treatment tools can be responsible for this insufficient condition. Ovarian cancer is the most lethal gynecological cancer type and has the fifth place for the deaths related to cancer within women [2]. In addition to dreary situation, overall survival rates of ovarian cancer have not improved noteworthy since 1980s [3–5]. But, the theory about serous, clear cell and endometrioid carcinomas of ovary originated from fallopian tubes could be the light at the end of the tunnel.

The lesions similar to ovarian serous carcinomas found in the fallopian tubes in women who have genetic tendency to ovarian cancer. These lesions could be the origin of the ovarian cancer and they could be cause of peritoneal cancer without ovarian cancer by spreading. In addition, TP53 mutation was found in tubal lesions, like high grade serous ovarian cancer [6, 7]. Supportive findings continued to come with a very large prospective cohort study known as the Nurses' Health Studies. According to this trial, women who had underwent tubal ligation had 24% lower risk of ovarian cancer compared to women who did not have this surgery [8]. The Swedish population-based cohort study showed that while salpingectomy causes 65% to fall of ovarian cancer risk, tubal ligation effects reduces 28% the same risk [9]. Subsequently, The Million Women Study (n = 1,278,783) proved the protective effect of tubal ligation from ovarian, tubal and peritoneal cancer [10]. A meta-analysis compared women who had hysterectomy for benign indications with salpingectomy and who had only hysterectomy. This powerful study with 30 years follow-up period showed that the salpingectomy significantly reduces the ovarian cancer risk after the surgery [11]. These findings especially tubal ligation effects on ovarian cancer risk reduction bring out the idea that ovarian cancer can be associated with retrograde menses [12] which will be a new investigation area.

In the light of the abovementioned literature, gynecologist should discuss with their patients about prophylactic salpingectomy who will have pelvic surgery. These procedures involve female sterilization, infertility surgery, and surely hysterectomies for benign indications. It is important to emphasize that salpingectomy reduces the risk of ovarian cancer but does not completely eliminate it.

Many women admit to clinicians for permanent contraceptive methods. They should inform about the success rates of other non-invasive contraceptive methods and the risk of regret related to permanent techniques. After all, bilateral salpingectomy should suggest to women who ask for permanent contraceptive methods. Furthermore, the worldwide popularity of bilateral salpingectomy increases compared to tubal ligation. A retrospective analysis showed an increase from 1 to 78% for prophylactic bilateral salpingectomy (PBS) instead of tubal ligation for last 5 years [13]. PBS increases the effectiveness in comparison with tubal ligation theoretically, as well as reduces the re-operation risks for ectopic pregnancy and hydrosalpinx [14].

Nowadays, almost all reproductive surgeries performed laparoscopically and hydrosalpinx is one of the fertility-related surgery indication. Detrimental consequences of hydrosalpinx for pregnancy put forth clearly by several trials. A meta-analysis investigated 6713 IVF cycles and showed that pregnancy rate was 50% lower in expectant mothers who had hydrosalpinx compared to women without hydrosalpinx. Moreover, miscarriage rate was higher in hydrosalpinx group [15]. Another meta-analysis focused on tubal factor infertility and determined that hydrosalpinx was the worst one. Pregnancy rate was 20% for women with hydrosalpinx and 31% for women with other tubal factors [16]. Fortunately, salpingectomy for hydrosalpinx before IVF cycle improved the implantation and pregnancy rates per transfer from 5% and 19% to 10% and 34%, respectively [16].

Hysterectomies with benign indications are the one of the chances for performing bilateral

salpingectomy and reduce the ovarian cancer risk. According to Cadish's decision analysis model, 225 hysterectomies with PBS exclude 1 diagnosis of ovarian cancer and 450 PBS added to hysterectomies save a life [17].

28.2.2 Salpingectomy or Salpingo-Oophorectomy?

Patient who will have pelvic surgery should be informed about PBS and prophylactic salpingo-oophorectomy (PBSO) and this counseling should be documented. Although PBSO is a very important risk reducing strategy for women with a genetic predisposition for ovarian carcinoma; PBSO does not eliminate ovarian carcinoma risk totally. Because, peritoneal carcinoma can develop after this prophylactic surgery.

On the other hand, serious concerns have arisen about PBSO. We know that the ovaries after menopause continue to produce androgens besides estrone and estradiol with a lower amount. In addition to that, androgens turn estrogen in the fatty tissue with aromatization. Removing this effect with PBSO in the young ages increased the all-cause mortality risk as in the Mayo Cohort Oophorectomy and Aging Study [18]. Nurses' Health Study proved the increased all-cause mortality and cancer-related mortality risk (16.8% and 13.3%, respectively) in women who had BSO. Especially, the risk was higher for patients who had this surgery before their 50s and never used additional hormone therapy [19]. Furthermore, surgery related to menopause raises the risk of cardiovascular disease, cancers other than ovarian cancer, cognitive impairment, and osteoporosis [20]. Protective effects of ovarian conservation decreased with age and it is just so minimal after 65 years [21]. Lastly, the risk of ovarian carcinoma after hysterectomies without PBSO is 0.1–0.75% and patient lost related to ovarian carcinoma is 0.03% [22].

Although we understand better the risks of early menopause, there are often clear indications for salpingo-oophorectomy for women with a gynecologic malignancy. Obesity, oral contraceptive use less than 1 year, nulliparity, not breastfeeding, dysmenorrhea, endometriosis, and polycystic ovarian syndrome may increase the risk of ovarian cancer by up to 4%. There are also advantages of PBSO for patient with endometriosis and tubo-ovarian abscess. The surgery might prevent re-operation risks and decrease endometriosis-related symptoms [23, 24]. Patients with pelvic adhesions are candidates for PBSO, as well [25]. The risk of residual ovary syndrome which is characterized by post-hysterectomy pelvic pain is high in these group. The incidence of residual ovary syndrome can reach from 0.9 to 3.4% [26].

28.2.3 Risks Against Benefits and Feasibility

Prophylactic bilateral salpingectomy as an additional procedure to hysterectomy or as an alternative to tubal ligation seems to be safe and does not increase the complication rates like fever, infection, blood transfusion, and re-operation [27, 28].

Regret and seeking alternatives for fertility after PBS ought to be discussed with patients who desire permanent sterilization. This is shared risk for all permanent contraceptive methods, as well [29]. Ovarian function is another concern about PBS especially procedures before IVF, whereas PBS does not affect ovarian function if it is performed properly [30]. Sahin et al. performed a prospective study with 131 patients who have ectopic pregnancy. Participants divided into three groups for treatment as methotrexate (MTX) only, salpingectomy only, and salpingectomy following MTX groups. There was no significant difference pre-treatment and three months after treatment on anti-Mullerian hormone (AMH) levels between groups, although the decreasing of AMH levels was detected on first month after treatment in salpingectomy groups. Researchers explained these results with compensatory increase of blood flow [31]. In a prospective randomized cohort study, ovarian reserve was compared after hysterectomy with benign indication between only hysterectomy group and hysterectomy with opportunistic salpingectomy group.

Patients who had only open abdominal hysterectomy was enrolled the study due to risk of ischemia-perfusion injury in laparoscopic surgery. After 6 months follow-up, there was no significant difference between groups for ovarian reserve parameters like AMH and ovarian volume [32]. Seventy-one women who had laparoscopic hysterectomy with PBS compared to ovarian function parameters like AMH, follicle stimulating hormone, antral follicle count and vascular parameters with 652 healthy women 3–5 years after operation. Results showed no significant difference between groups [33]. Another trial compared total laparoscopic hysterectomies with total laparoscopic hysterectomies with PBS. After 3 months follow-up, there is no significantly difference again about ovarian function, surgical risks, and complication rates [34].

Unfortunately, PBS does not totally eliminate the risk of ovarian cancer. Germ cell tumors, sex-cord stromal tumors, and other non-epithelial ovarian carcinomas might be arisen from ovaries after PBS. Clinicians have the obligation to discuss these risks with their patients and should not leave assess the ovarian carcinoma related signs and symptoms after surgery.

Eight trials compared PBS and tubal ligation between 2011 and 2018 with 21,709 participants in terms of success rates, blood loss, operative time, complication rates, re-operation and re-admission rates. Additional time for PBS ranges from 9 to 17 min. Researchers declared there was no significant difference between two methods for other parameters [13, 35–41].

Cadish et al. [17] investigated the surgical risk related to PBS after vaginal hysterectomy. Results of their study showed us that PBS after vaginal hysterectomy does not increase the complication rates significantly. Complication rate was 7.68% in only vaginal hysterectomy group and 7.95% in vaginal hysterectomy with PBS group [17].

A multicenter prospective and observational trial was designed by Antosh et al. [42] related feasibility of PBS after vaginal hysterectomies. Sixty-nine patients enrolled the study and PBS found feasible in 75% of participants. Mean required time for PBS after vaginal hysterectomy was 11 min [42]. It should also be underlined that the surgeons who attended the study were urogynecologists.

Prolonged operation time and extra instruments if they used might increase the cost slightly [43]. However, it is obvious that PBS is a cost-effective strategy considering possible adnexal surgery costs in the future if tubes left in place [17].

28.2.4 Surgical Technique

Salpingectomy defines the procedures that extraction of the fallopian tube from fimbriated ends to the utero-tubal junction. Residual fimbria extensions should be removed from the ovaries. Complete salpingectomy also preferred against fimbriectomy due to lesions which have the risk of ovarian carcinoma in the all tube [44]. But, when complete resection is not possible like cases with dense adhesions, fimbriectomy is better than nothing [45].

Antibiotic prophylaxis and thromboprophylaxis are not necessary particularly before laparoscopic PBS procedures. We prefer the use of an umbilical port for the laparoscope and bilateral lower quadrants ports for laparoscopic surgery. Uterine manipulator might facilitate the operation while it is not essential. Although it seems simple in theory, it is extremely important to recognize and to protect the infundibulopelvic ligament during the procedure. Resection should be made just below the tube for preserving the ovarian vessels and the ovarian function. Lastly, utero-tubal junction ought to be removed completely against the risk of cornual pregnancy which can be life threatening. If prophylactic salpingectomy performed after gynecological surgery with benign indication, it is not necessary to use a sterile bag for removal. But pathological analyses of the tubes are very important to uncover of any precursor lesions.

Finally, surgeons should not change the route of hysterectomy for the purpose of PBS. Vaginal hysterectomy is the most minimal invasive surgery compared to other techniques and should be the primary option.

28.3 Prophylactic Anti-prolapses Surgery

One of the common causes of hysterectomies is the pelvic organ prolapses [46]. Conversely, hysterectomy also might trigger the pelvic organ prolapses [47]. Risk of future prolapses is high after hysterectomies especially performed for pelvic organ prolapses (POP) [48]. Additional anti-prolapses surgery after hysterectomy may be a good idea for preventing future prolapses by restoration of Level 1 support [49].

28.3.1 Background and Benefits

DeLancey [49] identified the pelvic support with three levels. Level 1 occurs of cardinal and uterosacral ligament; Level 2 occurs of arcus tendinous fascia pelvis and endopelvic fascia; and Level 3 occurs of perineal body [49]. Surgical damage to the cardinal ligament, uterosacral ligament, innervations and vascularization of the pelvic floor muscles due to hysterectomy is concluded with weakening of Level 1 support and apical prolapses.

Marchionni et al. [50] analyzed retrospectively the data of 2600 women who had hysterectomy with benign indications to find out the prolapse rates over a 4-year period. The incidence of the vaginal vault prolapses after vaginal and abdominal hysterectomy was 12% and 2%, respectively [50]. A national cohort study from Denmark in which 178,000 women were investigated showed that prolapse rates after hysterectomy over a 40-year period [51] 3 times increased. According to Barber et al. (2014), the future prolapse risks range from 0 to 3.6% and the surgeons should counsel women who are going to be operated [52].

Hysterectomy is not a treatment option for women who have symptomatic prolapses. Pelvic organ prolapses need particular procedures for all areas at the same session [53]. The question is which patients need to be added the prophylactic surgery after hysterectomy?

Women with asymptomatic prolapses, women with symptomatic prolapses without any findings, and women with risk factors for POP are expected to benefit from prophylactic prolapses surgery. Vaginal delivery, obesity, chronic constipation and cough, family history, and connective tissue disorders are summarized as the risk factors for POP [53].

Apical suspension procedures are safe and effective operations for women who candidates to prophylactic prolapses surgery. McCall culdoplasty after vaginal hysterectomy and uterosacral ligament suspension after abdominal approaches have come forward as preferred techniques. However, there is no powerful recommendations about prophylactic prolapses procedures due to lack of data [54].

28.3.2 Risks Against Benefits and Feasibility

Prophylactic prolapses surgery has particular complication rates which range from 0 to 3.6% [52] and these operations should preserve for selected patients after considering risk and benefits balance.

Ureteral obstruction is the most common complications for both uterosacral ligament suspension (ULS) and McCall culdoplasty. The rates of ureteral obstruction are 4.5% for McCall culdoplasty and 1.8% for ULS [55, 56]. In general, ureteral complications are detected during surgery. Due to close relationship between the ureter and uterosacral ligament, cystoscopy is highly recommended after procedure. On the other hand, Rardin et al. (2009) compared to vaginal and laparoscopic approaches about apical prolapses surgery and found that ureteral obstruction rates 4% and 0%, respectively [57]. It might be another advantage of the laparoscopic surgery due to superiority on visualization. Uncommon complications of ULS are blood transfusion (1.3%) and pelvic organ injury (0.4%). McCall culdoplasty also have rectal injury (0.5%) and blood loss >500 mL (1.1%) risks [56, 58].

Prophylactic McCall culdoplasty and ULS prolong the surgery in acceptable limits. Gencdal et al. (2019) reported mean operation time is 74.3 min for total laparoscopic hysterectomy and

86.2 min for total laparoscopic hysterectomy with prophylactic McCall culdoplasty [59]. According to another trial, mean operation time for total laparoscopic hysterectomy with laparoscopic ULS is 102.5 min [60].

28.3.3 Surgical Technique

All culdoplasty procedures aim to restore uterosacral–cardinal ligament complex [61]. There is no proven superiority between these two techniques over each other. Surgeons might choose one of them according to their experience and talent.

We prefer no. 0 or 1 delayed absorbable suture material for McCall culdoplasty. First step of the procedure is identifying the ureters. Ureters should be palpated. After that Allis clamps can be used to locate the ureters at the 5 and 7 o'clock positions. Long Breisky retractors and head light for surgeon can be employed for maintaining the exposure. The first internal McCall suture is placed at the distal part of the uterosacral ligament (US). The suture should be continued with several bites on the posterior peritoneum until the opposite side. The suture is then placed to the opposite US. One or two more sutures might be placed at the proximal parts of US according to the first suture with 1 cm between each suture. The next step of procedure is placing the external McCall sutures. No. 0 or 1 delayed absorbable suture is placed posterior to vaginal mucosa and enters the abdominal cavity. After that, the suture is placed to US and exits through anterior vaginal mucosa. Finally, sutures can be tied with controlling intestine and omentum with index finger of first assistant surgeon. After all, bladder and ureteral jet flow should be checked via cystoscopy.

Uterosacral ligament suspension can be performed with both vaginal and laparoscopic approaches. Although it is according to the surgeon's experience, laparoscopic visualization is often better than vaginal techniques. First of all, surgeon should provide exposure and check the ureters. We prefer no. 0 or 1 delayed absorbable suture for uterosacral ligament suspension. After hysterectomy, 1–3 sutures can be placed US and attached to ipsilateral vaginal cuff. This step is repeated for counter side. Of course, cystoscopy for checking the ureters is the part of the procedure.

28.4 Prophylactic Cerclage

Prevention of preterm delivery is one of the issues without absolute solutions in modern obstetrics. Neonatal morbidity and mortality increased due to preterm delivery and pushes the health systems economically. Cervical insufficiency is one of the reasons of preterm delivery and the incidence is 0.1–1% of all pregnancies.

28.4.1 Background and Benefits

Deficiency of the uterine cervix to sustain a pregnancy in the second trimester without preterm premature rupture of membranes or uterine contraction is defined as cervical insufficiency [62]. Obstetric lacerations, conization, mechanical dilatation, congenital Müllerian anomalies, collagen and elastin deficiencies are the etiologies of the cervical insufficiency [62, 63].

Vaginal pessary is the only one non-invasive option for the prevention of preterm birth due to cervical insufficiency. However, the effect of vaginal pessary to prevent preterm delivery is not clear. Saccone et al. (2017) showed that vaginal pessary could not improve the obstetrics outcomes while increasing vaginal discharge in singleton pregnancies [64].

Cervical cerclage is the operative option for the prevention of preterm birth due to cervical insufficiency. Cerclage aims to increase cervical support and preserve pregnancy via strengthening sutures. Emergency/rescue cerclage and prophylactic cerclage are the types of cervical cerclage. Women who have cervical dilatation or prolapses membranes in the second trimester of pregnancy at high risk for preterm delivery and they are candidates for rescue cerclage. Conversely, prophylactic cerclage is an elective procedure and preformed based on history of cervical insufficiency.

Painless cervical dilation on physical examination in the second trimester and cervical length less than 25 mm before 24 weeks of gestation with a history of preterm birth are the indications for rescue cerclage. Women with history of cervical insufficiency and history of prior cerclage require prophylactic cerclage. Due to increasing effect for preterm delivery, cerclage is not appropriate for twin pregnancies and not recommended [62].

The success rate of prophylactic cerclage for the prevention of preterm delivery is very high. Take home baby ratio after abdominal cerclage is 95%. Vaginal cerclage follows abdominal ones with 73% success rate. Take home baby ratio without any intervention is only 33% [65].

28.4.2 Risks Against Benefits and Feasibility

Complications and risks of cerclage changes related to the time and type of procedure. Emergent or elective situation, cervical dilatations, and gestational age are the parameters. Premature preterm rupture of membranes is the most common complication and the rate is 38%. The infection rates for rescue and prophylactic cerclage is 12.7% and 4.7%, respectively [66]. Maternal septicemia and uterine rupture are rarely seen [67].

Abdominal cerclage with all risks of open surgery has higher complication rates compared to vaginal cerclage [68]. Hemorrhage, bladder and bowel injury, and rectovaginal fistula are the operative risks of abdominal cerclage. However, while operating a gravid woman, surgeon should consider pregnancy-related complications due to abdominal cerclage. But, prophylactic pre-conceptional transabdominal cerclage eliminates the pregnancy-related complications [69]. A prospective cohort study from the United Kingdom showed that prophylactic pre-conceptional transabdominal cerclage is more successful in preventing preterm delivery than first trimester abdominal cerclage with lower complication rates [70]. Fortunately, cerclage before conception does not affect the fertility [70, 71].

Both vaginal and abdominal cerclages are safe and feasible procedures in experienced hands. Abdominal cerclage also performed via laparoscopy. Laparoscopic approaches with superior visualization should be considered with high success rates and low risk especially in pre-conceptional period.

28.4.3 Surgical Technique

Cerclage can be placed by transvaginal or transabdominal route in order to prevent preterm birth. McDonald and Shirodkar techniques are adopted approaches for transvaginal cerclage. Ten to 14 weeks of gestation after getting results of first trimester, screening test might be the right time for placing prophylactic cerclage.

A single non-absorbable purse-string suture is placed at cervico-vaginal junction in the McDonald technique. In the Shirodkar technique, suture is placed at more proximal part of cervix after dissection of vesico-cervical mucosa. But, there is no superiority between these two techniques and different suture types [72].

However, prophylactic transabdominal cerclage should be reserved for women who have previous cerclage failure or anatomical limitations [73]. Placing suture at the level of internal cervical os and the lower risk of suture migration are the advantages of transabdominal route compared to transvaginal cerclage [74]. Transabdominal cerclage might be placed via laparotomy or laparoscopy. Although performing transabdominal prophylactic cerclage for gravid uterus is possible, pre-conceptional time is safer and more effective.

We prefer prophylactic laparoscopic cerclage before pregnancy in our institution. A 10-mm optic port and three 5-mm trocars are employed for operation. First step of surgery is the dissection of bladder from cervix. After that, the uterine arteries are identified. A 5-mm permanent tape with flat needles should be placed medial to uterine artery and lateral to venous plexus in order to prevent possible bleeding. After placing other ends of suture to opposite side, the suture can be

tied anteriorly. The operation ends with covering the visceral peritoneum [75].

28.5 Prophylactic Appendectomy in Obstetrics and Gynecology

Elective coincidental appendectomy is removing appendix during unrelated surgical procedure. Prophylactic appendectomy especially in obstetrics and gynecological surgery is an issue that has been debated for more than 60 years and it is still unclear.

28.5.1 Background and Benefits

Preventing a future possible appendectomy and appendicitis related complications are the benefits of prophylactic appendectomy. Due to lack of data related to cost-effectivity and changing beneficial effect according to age, patient selection should be individualized for coincidental appendectomy [76].

Estimated risk of appendicitis in women is under 7% [77]. The incidence of appendicitis is maximum between ages 10 and 19 and decreases with age [77]. According to Snyder [78], the greatest benefit was in patients younger than 35 years old who had coincidental appendectomy during unrelated gynecological procedure. Another conclusion of this study is limiting the prophylactic appendectomy in specific indications in women between ages 35 and 50. Moreover, their data did not support coincidental appendectomy for patients older than 50s [78].

Chronic pelvic pain is a condition that the benefit of prophylactic appendectomy is relatively more certain in gynecological practice. Chronic pelvic pain defines as pelvic pain that persists over 6 months and requires multidisciplinary management. Laparoscopic surgery can be good option for women who have chronic pelvic pain for diagnosis of endometriosis, uterine anomalies such as myomas and adnexal pathologies. In a retrospective cohort study, effectiveness of coincidental appendectomy during diagnostic laparoscopy in women with chronic pelvic pain was assessed. Patient with any pelvic pathology such as endometriosis or uterine anomalies was excluded from study. The study concluded that patients without any identifiable pelvic pathology benefited from prophylactic appendectomy compared to patient who did not have appendectomy during laparoscopy [79].

Women who will have pelvic or abdominal radiation or chemotherapy, women who will have major operations in which dense adhesions are anticipated postoperatively, and disabled patients who will have difficulty for explaining possible appendicitis symptoms also benefit from prophylactic appendectomy [76].

Patients with endometriosis are candidates for coincidental appendectomy if they will have an operation related to their symptoms, as well. The incidence of endometriosis in appendix in patients who suffering from endometriosis ranges between 9.3 and 39.0% [80, 81]. Although prophylactic appendectomy reduces pain significantly in patient with chronic pelvic pain, patient selection for endometriosis cases should be individualized. Full investigation including MRI before deep endometriosis surgery ought to be performed. If bowel endometriosis is detected, addressed surgery should be performed including segmental resection of bowel considering the benefits and harms to the patient. It should be kept in mind that reputable associations do not have precise opinions for coincidental appendectomy during endometriosis surgery. However, appendix should be evaluated during the endometriosis operations and if necessary, opinion of general surgeons should be requested.

Finally, the most controversial issue is appendectomy during cesarean section and during postpartum sterilization. Greatest benefit is in patients younger than 35 years old for coincidental appendectomy. These two surgical procedures seem to be compatible in terms of age.

28.5.2 Risks Against Benefits and Feasibility

Increased morbidity related to prophylactic appendectomy is shown in many studies [82–86]. There are also many studies proving that prophylactic appendectomy does not increase morbidity [87–89]. Although the issue is controversial, gynecologists are cautious about prophylactic appendectomy. This can be explained by the lack of definitive recommendations and medico-legal concerns. A study with one of the goals is to address these concerns was performed in Holland. Forty five cesarean delivery with prophylactic appendectomy and 48 cesarean delivery without prophylactic appendectomy were performed by obstetrics and gynecology resident physicians who were supervised by maternal fetal medicine faculty members. No increased morbidity was found between the two groups at the end of the study. Venous engorgement in pelvis, a fresh uterine scar, blood in the uterine and abdominal cavity, increased risk of ileus, bacterial contamination in manipulation of the bowel, increased blood loss, and increased operating time can be counted as justified concerns, as well [90–92].

In the light of abovementioned controversial literature, patient selection should be individualized for coincidental appendectomy in obstetrics and gynecological surgery and contribution of general surgeons should be requested in operation.

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29 Prophylactic Surgical Procedures in Plastic Surgery

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29.1 Introduction

Prophylactic or preventive surgery is mostly known as a type of surgery whose purpose is to prevent the risk of developing cancer in an organ or gland. Although the usage of the term mostly restricted to cancer prevention based on the genetic characteristic, besides the cancer prevention, there are wide variety of cancer-unrelated conditions that their progression into unwanted consequences or more complex future diseases can be prevented surgically.

Since the surgeries are usually permanent and irreversible, in addition to detailed workups and consultations, ethical, physiological, and psychological aspects of the procedure should be discussed with the patients before the procedure. The pros and cons, costs, time lost, and recovery must be carefully weighed by individuals as well. These considerations are usually less challenging in plastic surgery practice because rather than removal of an organ or gland, in most cases it is the only resultant skin scar of the body that should be taken into account. However, the problem and its solution can also be extremely challenging if the case is a congenital melanocytic nevus covering more than half of an infant's body that requires meticulous planning, multiple surgeries, and implant (tissue expander) replacements. It should be also kept in mind that, as a rule of thumb, surgical intentions in plastic surgery practice are mostly based on individual characteristics and needs, namely patient-tailored. Accordingly, surgeons should also carry on this demeanor in their prophylactic surgical practice by making patient-tailored risk and benefit assessments.

Undertaking a prophylactic surgery, however, does not certainly guarantee that the patients will never have cancer in the future. As discussed thoroughly at some point below in this chapter, it is now better known that certain type of cancers, rather than developing from congenital suspicious lesion, more likely tend to occur in the healthy skin of a genetically susceptible individual. While this may interrogate the indication of prophylactic surgery in certain instances, it also underlies the importance of the dermatologic surveillance that requires harmonic interdisciplinary interactions.

This chapter attempts to review plastic surgical prophylactic conditions under three main topics. First, "cancer-related conditions" mainly discusses the hereditary syndromes with skin manifestations in which cancer prevention can be achieved by recognizing and removing the certain type skin lesions and it also addresses some

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other sporadic conditions associated with the cancer development. Second topic accounts for well-known "premalignant lesions" in that some of their prophylactic surgical removal can be even lifesaving. And lastly "cancer-unrelated conditions" comprise certain benign conditions or injuries that are surgically targeted to prevent some kind of unwanted conditions, complications, or loss of function.

29.2 Cancer-Related Conditions

Cancer-related prophylactic surgical applications in plastic surgery mostly begin with identification of the skin or soft tissue lesions that are known to be at increased risk for developing cancer. Cooperation between medical departments is also important because, as being the largest organ, the skin overlaps the interest of multiple disciplines and either detection or follow-up of a lesion with increased cancer risk often requires strict dermatologic surveillance. Furthermore, patients suffering from hereditary syndromes are somehow more likely to need multidisciplinary treatment.

Suspicious changes of previous lesion or a newly identified suspicious lesion during the dermatologic surveillance can lead the surgeon to perform a prophylactic removal, or despite the follow-up recommendation of a dermatologist, the patient can seek surgery because of the fear of cancer.

The identification of premalignant skin lesions and treatment of such suspicious lesions through prophylactic excision might have played an important role in the efforts to prevent and cure skin malignancies. In the light of striking contrast between the sophistication of diagnostic tools, and the crudeness of preventive surgery, treatment of these lesions, nevertheless, has been remained problematic and controversial. On the other hand, these lesions are usually conspicuous aberrations that patients seek a way to get rid of cosmetically. However, the oncological concerns for complete removal of dysplastic tissue do not usually coincide with some elaborate procedures for concealment of these lesions such as shaving, peeling, curettage, or desiccation. When a patient is diagnosed with a premalignant skin lesion, there are two options to recommend: watchful waiting or prophylactic removal. If a strong family and social support is available and close clinical surveillance seems to be feasible, the recent trend tends to be in favor of the former way. In the face of diagnosed severe genetic instability and a report of strong family predisposition to malignant skin lesions, preemptive surgery might be lifesaving, keeping in mind, however, the malignancies not infrequently stem from normal-appearing skin in these patients.

29.2.1 Hereditary Melanoma and Atypical Mole/Nevus (Dysplastic Nevus)

Hereditary melanoma refers a spectrum of genetically inherited conditions which have an increased risk for developing malignant melanoma of the skin and/or other tissues. Cutaneous malignant melanoma (CMM) is a neoplasm arising from skin melanocytes (Fig. 29.1). It represents a small percentage of the overall skin cancers diagnosed each year (3%) but is accountable for an overwhelming number of the deaths (65%) resulted from the skin cancers [1]. Nevertheless, CMM is also a kind of malignancy that, if diagnosed early enough, almost yields 100% recovery. Since the 1950s, the incidence of melanoma has increased 340%; however, the death rate from melanoma has increased only

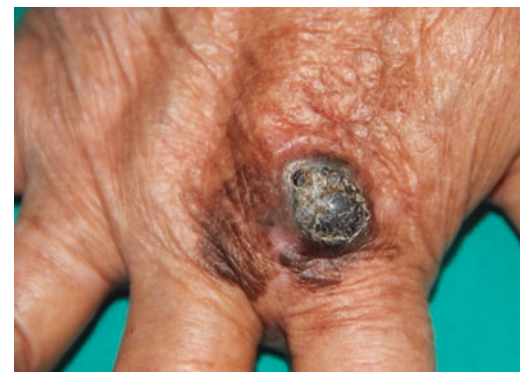

Fig. 29.1 Cutaneous malignant melanoma of the hand

150%, which has mostly been attributable to the early stage of diagnosis and more curable potential of the disease when detected at earlier stages [1, 2]. Many factors are known that increase the neoplastic transformation of the melanocytes. Ultraviolet (UV) irradiation, intermittent sun exposure (especially childhood sunburn), red or blonde hair, blue or gray eye color, Fitzpatrick skin types I and II, giant congenital nevi, atypical mole/dysplastic nevi, immunosuppression and genetic disorders, such as xeroderma pigmentosum, Li–Fraumeni syndrome, and *F*amilial *A*typical *M*ultiple *M*ole-*M*elanoma (FAMMM) syndrome constitute the most significant risk factors [3–6]. Increased awareness and surveillance of the abnormal and premalignant skin lesions [3] as well as recognizing patients at familial risk [7] has in part led to increased incidence of CMM detection at earlier stages, which plays an essential role to decrease the mortality of the disease.

Approximately 5–10% of all CMMs occur in families with hereditary melanoma predisposition [8]. This familial type of CMM was first described two centuries ago. In 1820, Norris (1820) referred his observations to as a "fungoid disease" and described a family in which two members had CMM and several relatives had large moles [9]. In 1952, Cawley reported CMMs in a father with his two children and suggested a hereditary basis for the occurrence [10]. Later in 1967, Anderson et al. described 22 similar families [11]. After a decade, Clark et al. (1978) presented the B-K mole syndrome characterized by the existence of numerous moles and increased risk of CMM formation among the family members [12]. Clinic and histologic properties described by Clark's studies gave rise to many controversies. Soon after, Lynch (1978) proposed a more accurate naming, FAMMM syndrome, to be given to the observations in association with a distinguishing cutaneous phenotype characterized by multiple large moles, irregular in shape, colored reddish-brown to pink, with evidence of pigmentary leakage, and with an apparent autosomal dominant mode of inheritance [13].

In the readings on the hereditary melanoma, besides the clinical terms such as dysplastic nevus syndrome [14], atypical mole syndrome [15] and Clark's nevus syndrome [16], marked variety of histopathological terminology, for example, active junctional nevus, melanocytic intraepithelial neoplasia, pagetoid melanocytic proliferation, atypical melanocytic proliferation or nevus with architectural disorder can be encountered. A National Institutes of Health (NIH) Consensus Conference in 1992 recommended the descriptive term "atypical mole/nevus" for the clinical diagnosis and the histologic term "dysplastic nevus" be replaced with "nevus with architectural disorder" and accompanied with a statement describing the presence of atypia (mild, moderate, or severe) [17]. However, abovementioned and some other recommendations of NIH has never been fully adopted by the medical community and the use of the appellation "dysplastic nevus" widely continues [18]. All these different nomenclature and descriptions advocated are to describe leading actor lesion of the hereditary melanoma. Furthermore, *atypical mole/nevus or dysplastic nevus* provokes controversies and discussions not only for its clinical and histological terminology, but also for its definition, progression, and management. Although there are several modified definition criteria made by various authors [12, 14, 17, 19, 20], an atypical mole/nevus is simply a mole that exhibits distinct clinical features from banal mole and shares common histological features with CMM. Some authors advocate abandoning the term "dysplastic nevus" [18] since it is not a clinical entity that is recognizable by a diagnostic criterion but can only be identified by histological examination [21]. Indeed, as shown by many studies, clinical diagnosis and the histologic properties of the common or atypical moles may not be correlated reliably [22, 23]. There are also some well-documented studies indicating patients with atypical moles, either sporadically [24–27] or with a positive family history [20, 28, 29], are at increased risk for developing CMM. However, in these patients, rather than inevitably progression of an atypical mole through sequentially higher grades of dysplasia and eventually into melanoma, it is shown that the most likely CMM development occurs on the healthy skin (de novo) or in the clinically typical

banal mole [19, 20, 30–32]. Furthermore, there is only little evidence indicating that the individual dysplastic nevus lesions transform into CMM at any higher rate than banal nevi [21]. This leaves the fundamental question (whether dysplastic nevus represents a premalignant or precursor lesion for CMM) unanswered and leads controversies for the management. Currently, it is better known that what really confers to increased risk for CMM are high total mole count and large mole size, both frequently encountered in the familial form [33–35]. Despite the ongoing debates and common traditional approximations, behaving atypical moles as precursors for CMM has greatly diminished since they rarely develop into CMM on their own [18, 36].

Identification of the properties of inheritance in hereditary melanoma was greatly accomplished by Lynch et al. [37] in the early 1980s. Segregation analysis performed by the authors supported the FAMMM syndrome as an autosomal dominantly inherited syndrome that displays variable expressivity and reduced penetrance. Phenotypic variations such as cancers other than CMM noted in the FAMMM syndrome also led to identification of an association with pancreatic cancer by Lynch and Fusaro in 1991 [38]. Kaufman et al. described Melanoma Astrocytoma Syndrome (MAS) after identifying concurrent familial CMMs and nervous system tumors in 1993 [39]. Since 1997, the Melanoma Genetics Consortium, GenoMEL, comprised of researchers worldwide, has been actively working on the genetics of familial CMM. Studies have shown that carrying inherited germline mutations in particular cell cycle regulatory genes such as cyclin-dependent kinase 4 (CDK4) gene on chromosome 12q14 [40, 41] or the cyclin-dependent kinase inhibitor 2A (CDKN2A) gene on chromosome 9p21 [42, 43] are considered to be major risk factors for familial melanoma. The frequency of *CDKN2A* mutations is more common than *CDK4* mutations (20–40% versus 2%) in melanoma-prone families [8] and the variable penetrance of these mutations is known to be modified by environmental factors (e.g., geographic location and sun exposure patterns) [44, 45], melanoma associated phenotypes and coinheritance of several specific interleukin-9, glutathione *S*-transferase theta 1 or melanocortin-1-receptor (MC1R) variants [46, 47]. *MC1R* gene, a low-risk melanoma susceptibility gene, partly regulates pigmentation phenotype that may act both dependently and independently of UV radiation to influence melanoma risk [48, 49].

NIH identified FAMMM syndrome as a clinical phenotype that requires to meet all of the following criteria for the diagnosis: (1) occurrence of CMM in one or more first- or second-degree relatives, (2) presence of high total body nevi count (>50) and multiple atypical nevi, (3) specific histologic features in nevi, including: asymmetry, subepidermal fibroplasia, lentiginous melanocytic hyperplasia with spindle or epithelioid melanocytes, variable dermal lymphocyte infiltration, and presence of shouldering phenomenon [17].

Management of patients with FAMMM syndrome has focused on the following issues: (1) intensive dermatologic surveillance at periodic intervals facilitated by diagnostic aids for early detection of CMM; (2) biopsy of suspicious lesions; and (3) preventive measures such as sun protection, self-examination, and nevi reduction for prophylaxis. The frequency of surveillance although depends upon degree of the risk (e.g., number of atypical nevi), however, most authors agree on that 6-month intervals starting from adolescence are adequate [4, 50–52]. Documenting a thorough family history of cancer, especially melanoma or pancreatic cancer is of utmost importance. Screening should also be offered to first-degree and selected second-degree relatives of the patient. Special attention should be paid to patient's description of the changes within the preexisting moles and to the newly formed pigmented moles. Moreover, physician should always keep in mind the controversial dilemma: although atypical moles are more likely to undergo malignant transformation when compared to banal moles, melanomas of FAMMM syndrome, however, often develop on normal skin. Baseline total body skin examination should include the sun-protected areas, scalp, genitals, oral mucosa, and nails with records of high-quality photographs. Because the patients may have many atypical moles, lesions exhibiting the

so-called "ugly duckling sign" should warrant special attention. Currently, majority of the clinicians use the standard "ABCDE" rules to evaluate pigmented moles. This refers to *A*symmetric shape, *B*order irregularity, *C*olor variability, *D*iameter greater than 6 mm, and *E*volution [4]. Patients at risk should also do complete self-examination at every 3 months, looking for any perceived changes in shape, borders, color, and size. The patient should be informed about the importance of skin self-examination, which has the potential to detect CMM at earlier stages and reduce mortality [53, 54], and he or she should know the warning signs of the CMM and the prophylactics (e.g., sun protection). Such an approach allows detecting melanoma in earlier stages, decreases unnecessary surgical mole removals and makes the patient and the physician psychologically more comfortable [36].

After detailed objective physical examination, recognized atypical moles should be evaluated by dermoscopy, a noninvasive technique that allows for inspection of skin lesions unobstructed by skin surface reflections with a high diagnostic accuracy (80–90%) [4]. Although ongoing controversies about their cost-effectiveness [55], more advanced techniques such as total body photography and sequential digital dermoscopy imaging have also been suggested [53] for CMM detection at earlier stages.

Traditionally, atypical moles/dysplastic nevi were considered as precursor lesions to CMM, and it has been common to recommend prophylactic removal of these atypical-appearing moles [36]. Today, while one group still supports treating atypical moles as "premalignant skin lesions" [56, 57], the others, in contrast, resist this approach since the most CMMs in patients with FAMMM syndrome often develop de novo [19, 58]. Some authors advocate futility of preemptive removal of stable or benign-appearing moles since this practice has not been shown to reduce the CMM risk meaningfully and associated with increased morbidity and costs (level of evidence, IV) [36, 45]. However, there are some scenarios in which prophylactic removal of the atypical moles can be recommended: lesions with diagnostic doubts, dealing with only a few [36], or numerous [59] atypical moles, lacking prior photographic records [60], visually inaccessible lesions during self-examination (e.g., those on genitals, scalp, and back) [36], and having concurrent cosmetic goals. Furthermore, prophylactic surgery may be sought by either the patient or the physician with the fear of missing CMM on self-examination or clinic follow-up [59]. It is clear that complete removal of a patient's nevi will not completely prevent CMM risk because of its propensity to occur de novo or in preexisting banal nevi, and the answer for the question "to what extent prophylactic excision would reduce long-term CMM in high-risk patients" remains unclear [59]. On the other hand, in such individuals, any suspicious lesions including changing atypical/banal moles or freckles and non-healing sores should be promptly excised and, in addition to appropriate surgical margin clearance, further surgical interventions such as sentinel lymph node sampling should be completed.

The association between pancreatic cancer and FAMMM syndrome has become evident, with an estimated risk 13–22 times higher than that of the normal population. It also multiplies in patients with mutated *CDKN2A* [50, 61]. This makes pancreatic cancer the second most common malignancy in the FAMMM syndrome patients with the mutation as well [62].

MAS syndrome associated nervous system tumors are extremely rare and may be linked to young age (<30) astrocytomas, peripheral nerve sheath tumors or meningiomas, which may or may not precede the formation of CMM [45, 63].

The role of genetic testing in familial melanoma is controversial, since the dermatological surveillance does not require much knowledge of the patient's *CDKN2A* gene mutation status. However, knowing the inherited *CDKN2A* mutation can offer predictions associated with pancreatic cancer risk, and therefore it may help providing early measures for such a malignancy that needs to be diagnosed earlier for the best prognosis. American Academy of Dermatology makes recommendation for genetic counseling referral according to individual status in the following criteria [64]: incidence of CMM in the

geographic location, the number of primary CMM in the patient, and the number of individuals with CMM in the family. Thus, at least, physician should consider genetic testing in situations in which CMM is diagnosed at young age, multiple primary CMM diagnosed in the same individual, existence of multiple relatives with CMM and other type of significant cancer (e.g., pancreatic cancer) history in the family.

29.2.2 BAP-1 Tumor Syndrome

BAP-1 tumor syndrome, described by Wiesner in 2011 [65], is considered as an autosomal dominant syndrome caused by germline mutations in *BAP-1 (BRCA1-associated protein-1)* on chromosome 3*,* which can give rise to several cancers including CMM, uveal melanoma, malignant mesothelioma, renal cell carcinoma, and somewhat specific lesions called melanocytic *BAP-1* mutated atypical intradermal tumors (MBAITs) [66, 67]. While MBAITs clinically resemble well-circumscribed, dome-shaped, reddish-brown to skin-colored benign intradermal nevi, histologically they exhibit aggressiveness similar to nevoid melanomas or atypical Spitz tumors [67, 68]. Although there is no sufficient evidence indicating their malignancy, in addition to at least biannual dermatological and annual ophthalmological surveillance, patients who have MBAITs with atypia or evolution should undergo prophylactical excision given that these patients tend to have more aggressive malignancies with higher tumor staging and metastasis risk (level 4 evidence) [67].

29.2.3 Cowden Syndrome

Cowden syndrome (CS*),* a member of *PTEN* (the phosphatase and tensin homolog) hamartoma tumor syndrome, is a multi-system disease in which germline *PTEN* gene mutations cause benign overgrowths of numerous tissues (e.g., gastrointestinal polyps, trichilemmomas, lipomas, mucocutaneous neuromas, oral papilloma, and vascular anomalies) and increased risk for malignancies of a number of the organs including breast (most common), thyroid, endometrium, and colon [69]. Basal cell carcinoma (BCC), squamous cell carcinoma (SCC), or carcinoma of Merkel can rarely be seen as malignant skin manifestation of CS [70]. However, more recently, even if yet not included in the diagnostic criteria of the CS, it has been postulated that the CS patients tend to have increased risk for CMM [71, 72]. Although current guideline recommends dermatologic surveillance only if needed, CS patients frequently seek care for many of their socially disabling benign skin manifestations. Some authors recommend dermatologic surveillance at the time of the diagnosis and repeatedly based on the individual needs [73] that may require prophylactic excision of suspicious lesions.

29.2.4 Gorlin–Goltz Syndrome

Gorlin–Goltz syndrome (GGS) is a rare autosomal dominant neurocutaneous syndrome with well-defined diagnostic criteria [74]. Studies have shown GGS be resulted from mutations in *PTCH1, PTCH2,* or *SUFU* genes which encode hedgehog signaling pathway for growth control and tissue differentiation [75]. Early onset BCCs, palmoplantar pits, odontogenic keratocytes, medulloblastoma, and calcification of falx cerebri constitute some of the hallmark disorders of the GGS (Fig. 29.2). Patients with GGS may develop from a few to several hundreds of BCCs during their lifetime. This warrants special attention for dermatologic surveillance. Although new promising medical therapy modalities are available in treatment options [76], surgical excision is still mainstay of the curative treatment of suspicious lesions and newly occurring or recurrent BCCs.

Similar to GGS, both very rare genodermatoses, *Bazex-Dupré-Christol Syndrome* (BDCS) and *Rombo Syndrome* (RS) possess early onset BCC as a common malignant skin manifestation. Apart from BCCs, BDCS exhibits hypotrichosis, follicular atrophoderma, hypohidrosis, and milia. While males have a propensity of having more severe symptoms, lack of evidence of male-to-male transmission has led to the consideration that BDCS is inherited in a dominant X-linked

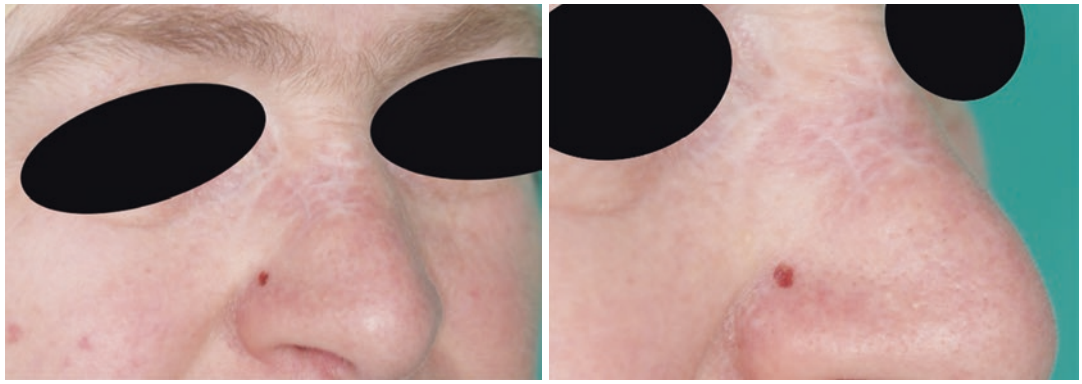

Fig. 29.2 Gorlin–Goltz syndrome with new BCC on right ala. Note the previous excision scars on the dorsum of the nose

pattern. On the other hand, RS may also exhibit milia, hypotrichosis, and vermiculate atrophoderma, but it has several distinct entities as well, such as trichoepitheliomas, cyanosis of hand and feet, and autosomal dominant inheritance [77]. Dermatological surveillance constitutes the most important modality to detect BCCs and trichoepitheliomas, the latter also has been shown to have a potential for malignant transformation [78].

29.2.5 Muir–Torre Syndrome

Muir–Torre syndrome (MTS) is a rare autosomal dominant disease with a genetic predisposition to sebaceous neoplasms (adenomas, epitheliomas, carcinomas, keratoacanthoma with sebaceous differentiation or cystic sebaceous neoplasm) and visceral malignancies (e.g., colorectal adenocarcinoma). MTS is caused by germline mutations in *MSH2* (Mutator S Homologue-2), *MSH6*, or *MLH1* (Mutator L Homologue-1) genes of the DNA mismatch repair system and is also considered as a subtype of hereditary nonpolyposis colorectal cancer (HNPCC) [79]. Diagnosis can be made as early as 21 years old of age and is largely determined with the existence of at least 1 sebaceous neoplasm and at least 1 internal organ cancer at some point in the patient's life without other contributory factors, such as radiotherapy or AIDS [77]. Sebaceous neoplasms usually present with benign properties, such as pinkish to yellow color, well-circumscribed dome or nodule

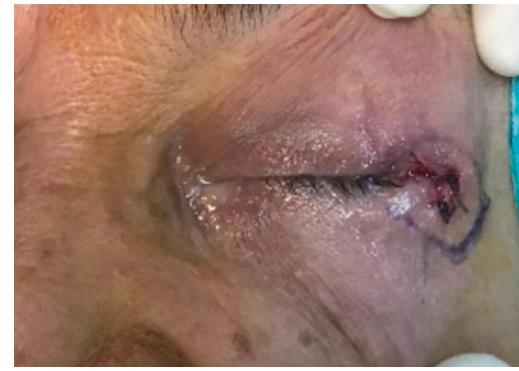

Fig. 29.3 Sebaceous carcinoma involving both eyelids. Patient eventually underwent orbital exenteration because of the extensive involvement

shape, and central umbilication or ulceration. While sporadic sebaceous neoplasms most likely occur in head and neck region, those tumors located inferior to the neck usually indicate MTS [80]. Sebaceous carcinomas are typically benign-looking lesions and since they are anticipated to encounter around the periocular region (Fig. 29.3), however, unusual carcinomas located elsewhere of the MTS patients may be misdiagnosed initially [81]. It is recommended that benign sebaceous lesions be treated with prophylactic surgical excision for following reasons: (1) if an individual has a sebaceous neoplasm, particularly adenoma, MSI (microsatellite instability) gene analysis and immunohistochemistry testing should be performed to elucidate whether gene products such as *MSH2*, *MSH6,* and *MLH1*

are present in the tumor. Combinational loss of staining of these gene products may have up to 100% predictive value for MTS diagnosis [79, 82]. (2) Such MTS diagnosis preceding visceral malignancies can provide screening and prophylactic treatment opportunity, and (3) benign appearance of these lesions may cause interventional delays for such an aggressive sebaceous carcinoma or precancerous lesions like keratoacanthoma [79]. However, chemoprophylactics and several non-surgical treatment options are also available for the cutaneous manifestations [81].

29.2.6 Porokeratosis

Porokeratosis is a familial disease characterized by keratotic plaques or annular plaques with elevated borders, which result from disordered progression of the epidermal cells. Clinically, six different variants have been described, all that have the potential to undergo malignant transformation mostly into SCC or less likely into BCC [77]. Histological hallmark of porokeratosis is cornoid lamella which is a tightly packed column of parakeratotic cells with varying degree of dysplasia exhibiting clones [83]. Sun protection, regular dermatological follow-ups, various non-surgical options for keratotic plaques, and excision of the suspicious lesions constitute the mainstay modalities of the management [83].

29.2.7 Xeroderma Pigmentosum

Xeroderma Pigmentosum (XP), meaning "dry pigmented skin," is an autosomal recessive disorder characterized by excessive photosensitivity, pigmentary changes, early onset of skin aging, and increased risk for skin malignancies, such as SCC, BCC, and CMM. XP has several subtypes mostly resulting from different gene mutations of nucleotide excision repair system, which play a key role in skin cancer prevention by correcting UV-induced DNA damages in skin cells. XP patients are classified into complementation groups (XP-A to G and XP-V) according to mutations they carry in the following genes: *XPA, XPB, XPC, XPD, XPF, XPG* or *POLH*. These gene mutations may lead to SCCs or BCCs to occur as early as 8 years of age [77]. Moreover, XP patients have an estimated 10,000-fold increased risk of nonmelanoma skin cancer and a 2000-fold increased risk of CMM below the age of 20 years [84]. Neurologic deficits can accompany the disease in about a quarter of patients and other internal malignancies involving blood cells, eye, uterus, breast, and gastrointestinal tract can be encountered (Fig. 29.4). Management requires multidisciplinary approach including dermatology, ophthalmology, neurology, genetics, and support groups. Extreme caution to minimize sun exposure, detecting skin changes in earliest stages, and proper surgical or non-surgical treatment of suspicious, precancerous or malignant lesions not only improve the quality of life, but also increase the life expectancy [85].

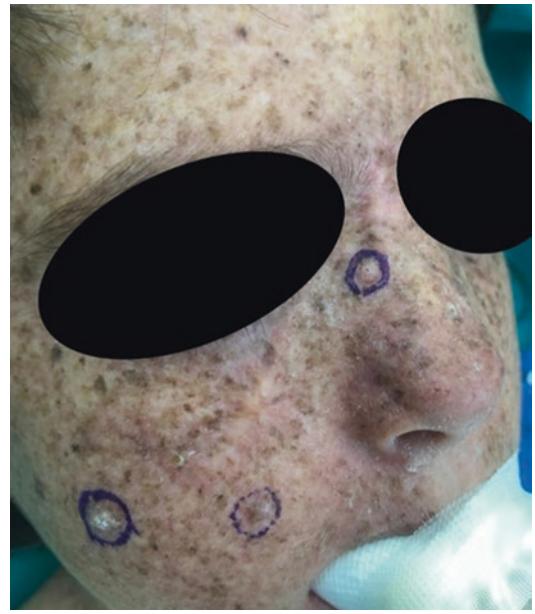

Fig. 29.4 Suspicious lesions on the face of a 7-year-old girl with xeroderma pigmentosum

29.2.8 Epidermodysplasia Verruciformis

Epidermodysplasia verruciformis (EV) is a rare, autosomal recessive genodermatosis, which pre-

disposes susceptible individuals to developing SCC when infected by certain HPV types (especially type 5 or 8) that are, however, normally considered to be harmless for the general population [86]. Although precise mechanism of the disease has yet to be discovered, it has been elucidated that mutations in the transmembrane channel genes (TMC6/EVER1 or TMC8/EVER2) make individual extremely susceptible for HPV infections [87]. EV often presents on the sun-exposing areas during infancy or childhood as warty or pityriasis versicolor like lesions with reddish squamous lesions or scaly, hypopigmented, brown-reddish macules. An acquired form of the disease, also sharing common clinical features with EV is known to be caused by HIV infection or immunosuppressive therapy and differs in its pathological mechanism and lacking heritage. Management, like most of the other genodermatosis, requires strict sun protection and dermatological surveillance with proper removal or ablation of the suspicious or precancerous lesions.

29.2.9 Breast Implant-Associated Anaplastic Large Cell Lymphoma

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is an uncommon T-cell lymphoma that typically presents with spontaneous periprosthetic effusion or capsular mass in the neighborhood of the breast implants placed for either cosmetic or reconstructive purposes [88]. Although it was first described in 1997 [89], increasing incidence of the disease led US Food and Drug Administration (FDA) in 2011 to communicate about the risks of BIA-ALCL and warn the women with the certain type of breast implants that they are at risk for developing this disease. By January 2020, FDA has been identified a total of 733 case worldwide, including 36 deaths attributable to the disease [90]. Currently, the development of the BIA-ALCL seems to be associated with a chronic inflammation including a complex interaction between the textured outer shell of the breast implant, bacterial contamination (biofilm formation), immune response, and patient genetics [91]. Textured breast implants were developed in response to search for more stability via a more adherent surface in the breast pocket, and it seems that they not only cause higher load of biofilm formation, but also by allowing tissue ingrowth, they contribute to the chronic inflammation eventually resulting with T-cell predominant infiltrate and lymphomagenesis in which the malignant transformations of immune cells usually take place in 7–10 years [92–95]. Diagnosis can be challenging. Depending upon the clinical presentation, fine-needle aspiration of the periprosthetic fluid accumulation (60–90%) or ultrasound-guided or open biopsy of the pericapsular mass (10–40%) may be required for cytologic evaluation, flow cytometry or immunochemistry [95, 96]. Treatment involves en bloc surgical explantation of the implant with the capsule, plus for advanced stages (II-IV), considerable lymphadenectomy and/or adjuvant chemotherapy, and radiotherapy for residual or unresectable disease [88, 97]. The National Comprehensive Cancer Network also recommends prophylactic removal of the normal-looking breast implant due to some cases of incidental disease findings in the contralateral side [97]. Complete surgical extirpation of the implant, capsule and additional near involvements yields excellent overall prognosis [88].

There have been several crises in the historical evolution of breast implants [98, 99]. These cycles including safety warnings, health concerns, recalls, restrictions, suspensions, moratoriums, and market withdrawals [98–106] have markedly impacted on more than ten million global implant carriers not only by psychological stress and panic, but also via having revision/removal surgeries [106]. In July 2019, BIA-ALCL-induced textured implant crisis has lastly caused voluntarily worldwide recall request of certain type of textured breast implants by FDA [105]. However, although asymptomatic carriers of these implants have not yet to be recommended to undergo prophylactic implant removal by any regulatory agency or medical society, it seems more data is required to make more accurate judgement for maximum patient safety and

comfort [105, 106]. Besides the ongoing crises, anticipating an increase in number of the patients worldwide as a result of increasing awareness of BIA-ALCL is not difficult. Nevertheless, accumulating knowledge from new data and further studies addressing BIA-ALCL will continuously evolve the understandings of diagnosis and treatment for the optimal patient safety, which may further involve implant removals on prophylactic basis even if it is not desirable by any party of the BIA-ALCL-induced implant crises.

29.2.10 Marjolin's Ulcer

Marjolin's ulcer (MU) is a cutaneous malignancy which was first described in 1828 by French surgeon, Jean Nicolas Marjolin, as ulcerations with dense villi arising within a burn scar [107]. Indeed, while it mostly arises from longstanding burn scars (1–2% of all burn scars, Fig. 29.5) [114], other chronic inflammatory skin conditions such as traumatic wounds, pressure sores, radiation dermatitis, venous stasis dermatitis, hidradenitis suppurativa, and chronic osteomyelitis sinuses can also end up with MU [108]. Typically, it occurs next to a chronic wound as a rapidly growing, foul-smelling, non-healing ulcerative lesion with elevated borders [109]. Exophytic granulation tissue, bleeding, regional lymphadenopathy, and superinfection can also accompany the classical presentation [110]. There are several theories for the malignant transformation of the wound cells. One theory suggests the continuously re-epithelizing state of the wound may cause overstimulation of the cell proliferation that can make the cells more prone for having spontaneous mutations [111]. Furthermore, likely deficiency of immune cells, which play important role for foreign antigens, in such a wound may lead the malignant cells to escape from immune system detection [112]. One other theory blames accumulated toxins in the chronic wounds for potential mutagens [113]. Classification of the MU depends the time from initial wounding. Although cancerous conversion typically takes more than 30 years, there are also an acute form in which the transformation takes place only in 12 months [114]. While SCC is the most common histological type of cancer in chronic wounds, BCC, which is most common in acute form, CMM, sarcoma, and some other type of cancers can also be detected [115]. MU has more aggressive behavior than other SCC etiologies. More than a quarter of the diagnosed patients have regional lymph node metastasis that means poor prognosis and death in the next 2–3 years [116]. Treatment should be radical and include wide local excision with clear margins, regional lymph node dissections, and even amputations of the limbs with neurovascular involvements [114]. Early detection and planned replacement of the suspicious chronic wounds by unscarred, healthy skin/soft tissue coverage is an

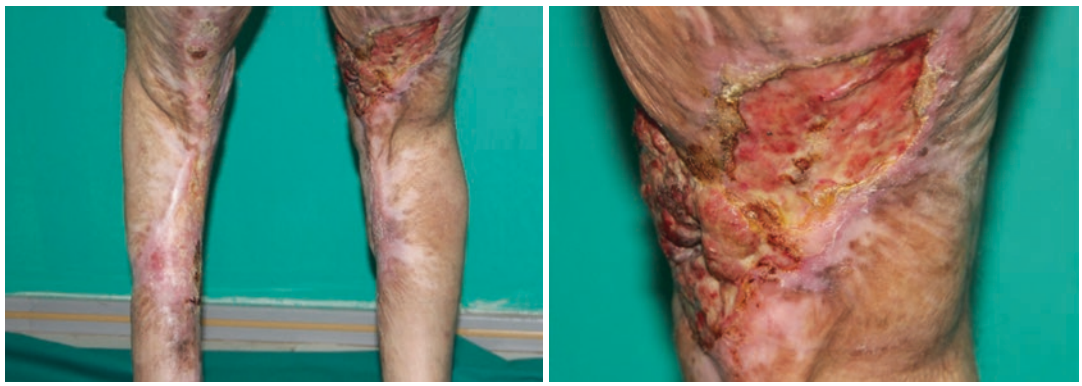

Fig. 29.5 Marjolin's ulcer in the burn scar 27 years after the initial injury. Undifferentiated pleomorphic cell sarcoma was diagnosed after the wound biopsy. Lymph nodes also revealed metastases following regional lymphadenectomy

important prophylactic intervention to prevent them turn into MU.

29.3 Premalignant Lesions

Premalignant or precancerous lesions, which are commonly encountered in dermatology and plastic surgery practice, conventionally, include the clinically and histologically recognizable skin lesions, which have the potential to harbor or progress into invasive skin tumors, such as CMM, SCC, and BCC.

Histologic examination can classify these lesions based on their origin in the skin (e.g., dermal, epidermal, follicular, or melanocytic). Besides, knowing the predominant location of these lesions also allows to make predictions about their natural progression or evolution, and eventually, accurate clinical-pathologic correlation for the proper management.

As clinical evaluation is replaced by microscopic and molecular detection of tissue behavior, surveillance of tissue specimens will lead the decision for the timing and extent of prophylactic interventions for premalignant skin lesions.

Here we discussed the most common forms of premalignant lesions among the numerous skin and mucosal proliferations and put emphasis especially on to prophylactic surgical interventions.

29.3.1 Solar Lentigo

Solar lentigo (SL) is a keratinocytic lesion which occurs on the body areas with the background of chronic sun exposure, such as face and dorsal hands, and resulted from local melanin accumulation in the keratinocytes following melanocytic proliferation. They are commonly seen typically after the age of 40 and can be oval, round, or irregularly shaped or tan to dark brown-black colored macules, also known as "*old age spots"* or "*senile freckles."* On occasion, melanocytic hyperplasia in some lesions may give rise difficulties in differentiating them from *lentigo maligna (LM),* which is a subtype of *melanoma* in situ characterized by proliferation of atypical melanocytes along the basal epidermis. Because of the likely evolution of SL to LM, some authors suggest naming these borderline lesions as "*unstable solar lentigo"* regarding their histologic features such as increased melanocytic proliferation confined to SL borders and lack of nuclear atypia [117, 118]. If left untreated, LM can develop into a variant of CMM, termed *lentigo malignant melanoma (LMM)* which also has common prognostic features as CMM. A recent review showed up to 30–50% of untreated LMs cases will progress to LMM, with a latency period varying from 10 to 50 years [119, 120]. This highlights the importance of dermatological surveillance which is mostly based on clinical and dermoscopic features and confirmed by biopsy and histopathological assessment. While SL, as being a benign and common lesion, can be dealt with a wide variety of non-surgical approach, suspicious or unstable solar lentigines are suggested to be removed with warranted clean surgical margins [118]. However, LM requires more aggressive treatment which is surgical excision with at least 5-mm, preferably 10-mm clinical margin [119].

29.3.2 Congenital Melanocytic Nevus

Congenital melanocytic nevus (CMN) is an abnormal but benign collection of nevus cells within the skin at birth. While it can be a small (<1.5 cm) lesion as seen in the 1% of neonates, it can also reach gigantic dimensions to cover 80% of the total body surface (Fig. 29.6). CMN syndrome is proposed by some authors where any extra-cutaneous systems involved [121]. Like many birthmarks, it results from in utero mutations. For a single CMN, even if it is difficult to determine the exact causative mutation, currently a series of genes such as (*NRAS, BRAF, MC1R, TP53, and GNAQ)* may be suspected. However, in patients with multiple CMN or CMN syndrome, post-zygotic *NRAS* mutations can be detected as many as 80% of the cases [122]. CMN is permanent, grows in proportion to the child, and occupies the associated territory and puts newborns with CMN at increased risk

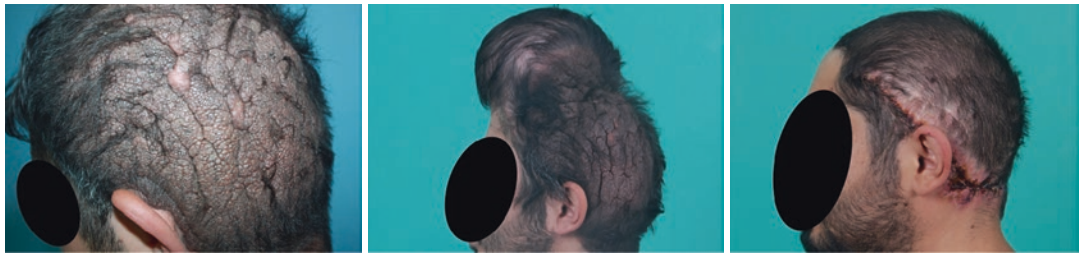

Fig. 29.6 Congenital melanocytic nevus of the scalp. The lesion was completely removed after two sessions of tissue expansion

for CMM. While single small birthmark lesions harbor very low risk for CMM and the overall incidence figure for all CMN is about 1–2%, CMN with approximated projection greater than 40 cm at adulthood and accompanied by multiple small CMNs has an estimated lifetime risk at 10–15% [123–126]. Because of the very low risk of MM development before adolescence, for small and medium CNS, regular dermatologic follow-ups are recommended rather than prophylactic excisions solely based on malignant transformation concerns [127]. However, there may be a wide variety of other important reasons for having a childhood term prophylactic excision, such as itching, irritation, psychosocial concerns, functional problems, and high level of parental anxiety. A review of surgical management of large and giant CMNs is beyond the scope of this chapter. To date, there is no good evidence that removal of such lesions reduces the risk of MM, probably because of likely impossibility of complete removal of every single nevus cell and potential of other visceral involvements. Despite this, some authors advocate experiencing fewer cases of MM in those who undergone surgery [128].

29.3.3 Blue Nevus

Blue nevus (BN) is a neural crest derived, melanocytic neoplasm which is composed of pigmented papule, plaque, or nodules with bluish-gray or bluish-black color. BN can occur at any age but is most commonly encountered at young adulthood. *Common BN* is a benign variant of BN which is mostly found on dorsal aspect of extremities, scalp, and buttocks and typically seen in children and young adults, especially in girls. *Cellular BN,* as being another benign variant, can be present at any age and most commonly seen in buttocks, sacrococcygeal region, scalp, and face. It can also be present at conjunctiva, orbit, breast, and subungual region, and although rare, it can reach up to 10 cm. *Malignant BN,* meanwhile, was first used to describe MM arising from benign BN variants [129]. Later, this term has also been suggested for the de novo MMs that share common histologic features with BN and MMs that arise from previous excision site of BN [130, 131]. *Atypical BN* describes histologically borderline, rare cases between benign variants and malignant BN [132]. Since the malignant BN has similar prognostics with CMM and may occasionally supervene on benign variants, it warrants special attention. However, even though the prophylactic removal of benign BN variants is not recommended, any sudden changes in size, color, or borders of the BN requires prompt excision [133]. In case of excision requirement of the benign variants for any other reason, excision with warranted clear margins prevent recurrence and occasional local aggressiveness of the disease.

29.3.4 Spitz Nevus

Spitz Nevus (SN) is a benign neoplasia of melanocytes, which may cause diagnostic errors and uncertainties due to several histologic features that resemble those of CMM. After long debates, currently, there has been a tendency to classify these lesions in three types [134],

which are sometimes still difficult to differentiate one from another: (1) Conventional SN is the benign form which mostly encountered in children and young adolescences with a size usually <10 mm. It typically presents as a solitary, well-defined dome-shaped papule or mass with a wide range of color properties such as pink, brown, tan, or red. While it can be found anywhere in the body, there is a predilection for head and neck for children and lower libs for adults. (Fig. 29.7a). (2) Atypical SN represents intermediate category which denoted for its uncertain malignant potential. Unlike the conventional form, these lesions generally tend to be asymmetrical, >10 mm in diameter, irregularly bordered, and sometimes ulcerated. (3) Spitzoid melanoma constitutes the malignant form of the SN. Although rare in children, most CMMs diagnosed in childhood are spitzoid melanomas which have more favorable outcomes when compared to adult CMMs. Even if SN is mostly diagnosed in children and adolescences, however, SN encountered in adulthood warrants special considerations since the advancing age steadily increases the malignant transformation potential of the SN [135]. Spitzoid melanomas are commonly occur on head and extremities (Fig. 29.7b). They are usually amelanotic, nodular lesions that can resemble hemangiomas, xanthogranulomas, or BCC [136, 137]. While it is beyond dispute treating diagnosed spitzoid melanoma as CMM, managing conventional SN is controversial. Some authors advocate prophylactic excisions of all SN [138]. In contrast, some others recently have suggested regular follow-up only for those under 12 years of age with no atypical clinic or dermoscopic features, given that the high spontaneous involution or transformation to other common melanocytic lesions of the conventional SN [139]. After 12 years of age, complete surgical removal or, alternatively,

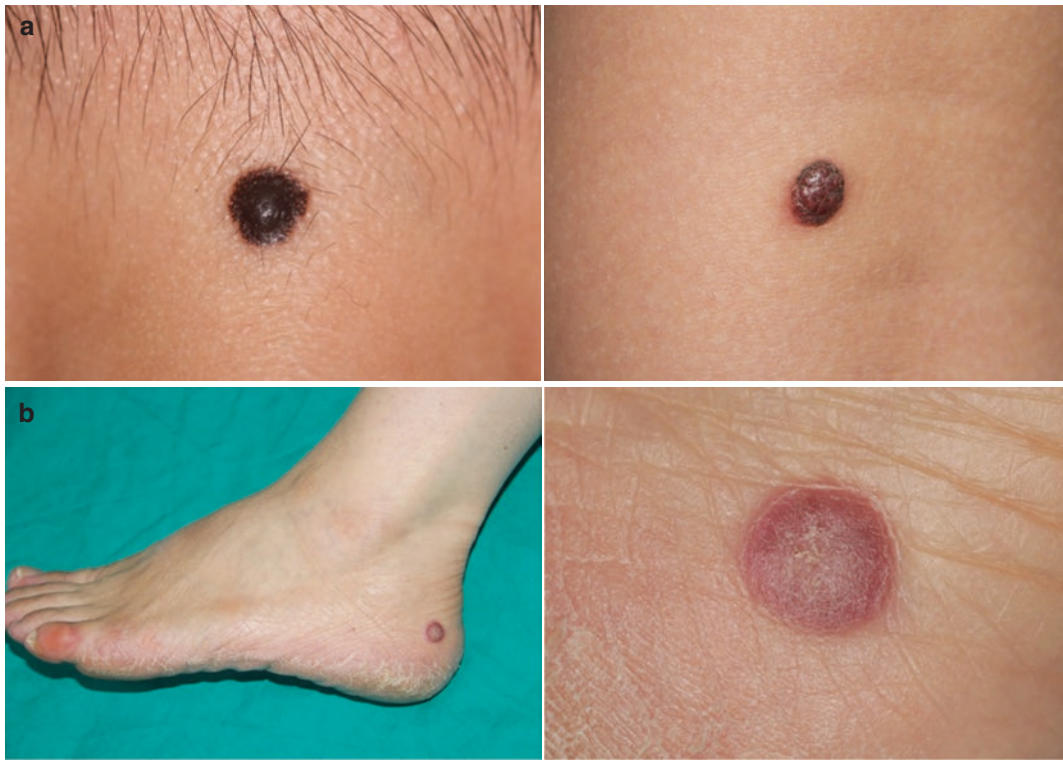

Fig. 29.7 (**a**) Common Spitz nevus in the glabella (left) and popliteal pit (right) of a 6- and 9-year-old patients, respectively. (**b**) Spitzoid melanoma on the heel of a 47-year-old female

digital monitoring should be performed until stabilization of the SN [140]. SN exhibiting atypical properties at any age mandates prompt excision with assurance of clear margins [140, 141]. Some authors also suggest sentinel lymph node biopsy for atypical SN [142].

29.3.5 Halo Nevus

Halo nevus (HN) is a pigmented nevus surrounded by a depigmented ring, which may be seen approximately 1% of the population, typically on the back of the children and young adults [143]. As the depigmented circle appears around, this usually leads to beginning of the regression in the nevus, which may ultimately result in complete disappearance of the nevus. Traditionally, since the HN was considered dysplastic, prophylactic excision was the preferred treatment of choice [144, 145]. However, as several studies have shown that most of HNs are not histologically dysplastic, surgical removal has only been recommended for cosmetic reasons, unless the HN has suspicious clinic features that can mimic MM [144, 146]. Although this halo phenomenon often related to benign acquired nevi, halos can also occur around a several lesions including CMM and BCC [144]. Even if the association of the halo phenomenon with CMM is extremely rare, excision should be preferred in case of clinical suspicion [146, 147].

29.3.6 Nevus Sebaceous

Nevus sebaceous (NS) is a congenital hamartoma that combines different abnormalities of the skin and skin appendages, such as hair follicles, sebaceous and apocrine glands. It often appears at birth or in infancy and mostly locates on head and neck region. Characteristically, it presents as a well-circumscribed, round, oval or linear, tan to yellowish-brown colored plaque lesion ranging in size from 1 to over 10 cm which grows proportionally with the patient (Fig. 29.8). Based on some studies, it is believed that to be an androgen-sensitive neoplasia [148]. NS may develop into

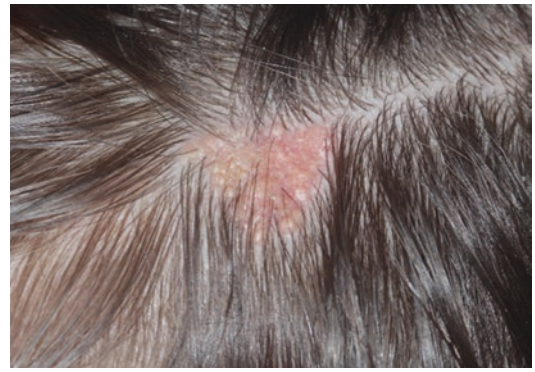

Fig. 29.8 Sebaceous nevus of the scalp

some benign tumors such as trichoblastoma, syringocystadenoma papilliferum, trichilemmoma, apocrine adenoma as well as malignant tumors including BCC, SCC, sebaceous and apocrine carcinomas [149]. Although the incidence of 6–50% of BCC in adults cited in studies from 1962 and early 1980s, this has not been supported in more recent studies [150]. Nevertheless, even though BCC still seems to be the most common malignant tumor, the malignant transformation rate is thought to be quite rare in childhood (1%) [148, 151–153]. This also adds some debates on prophylactic excision of lesion during childhood [150], while the definitive treatment of the lesion is full-thickness excision [148].

29.3.7 Actinic Keratosis

Actinic Keratosis (AK) or solar keratosis is a very common skin disease caused by chronic sun damage. It typically presents as rough-textured, small (3–6 cm), erythematous, scaly papules. Approximately 75% of the lesions locate on chronic sun-exposed areas such as face, scalp, neck, and dorsum of hands and forearms [154]. Age, male gender, skin type (Fitzpatrick I and II), ultraviolet exposure, sun-bedding, immunosuppression, and genetics (e.g., xeroderma pigmentosum) are major significant independent risk factors [155]. It is well-known that UV irradiation causes dimers of thymidine in DNA and RNA that produce mutations of the telomerase gene resulting with abnormalities in keratinocyte

proliferation [156]. This abnormal growth of the keratinocytes has been shown to progress into SCC in some cases; however, it is difficult to predict which AK lesion will show this progression. The risk is directly related to the number of the AK and timing of the appearance [157]. If left untreated, it is shown that 10-year incidence rate of SCC progression will be around 10% [158, 159]. This especially puts emphasis on the early diagnosis and treatment for preventing progression to SCC. Indeed, there are numerous effective non-surgical therapy modalities for the treatment that reserve the surgical excision option for only those which have high suspicious features for SCC, diagnostic uncertainty, or resistance to non-surgical treatment [160, 161].

29.3.8 Keratoacanthoma

Keratoacanthoma is a somewhat borderline neoplastic lesion that arises from hair follicles and typically occurs on the sun-exposed areas of the elderly. While some authors advocate it be classified as a low-grade SCC subtype regarding its metastasis and tumor-related death potential, others believe that because of the self-regressing feature of the lesions, KA should essentially be considered as a benign lesion that may transform into SCC (Fig. 29.9) [162, 163]. KA usually appears as minute papule and rapidly (in weeks) becomes dome- or bud-shaped, well-demarcated, umbilicated nodule with a hyperkeratotic, keratin-filled plaque in it [164]. Controversies persist for the management of KA. A wait-and-see for regression approach may not be rational, unless the clear signs of involution are identified early, since the final size of the lesion and the potential disfiguring scar after regression is not predictable. Therefore, whenever possible, surgical excision with clear margins is the gold-standard modality of treatment [164]. However, although its efficacy is limited, intralesional chemotherapy may be attributable as a second-line

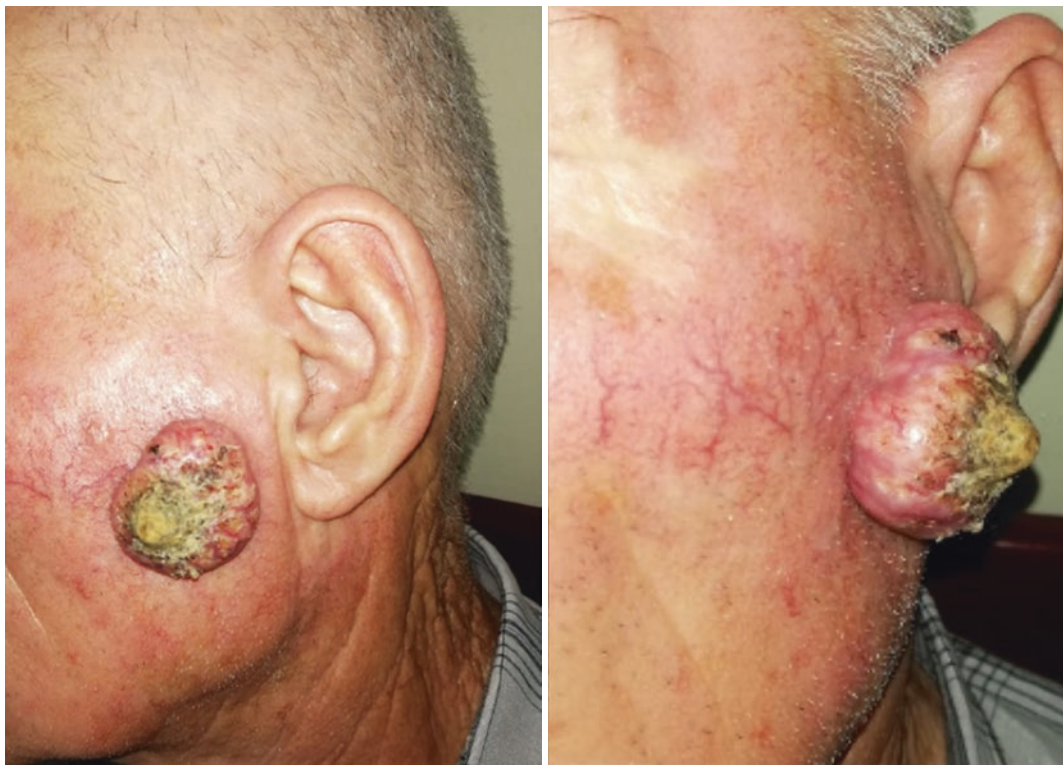

Fig. 29.9 Squamous cell carcinoma of the preauricular region arising from keratoacanthoma

treatment choice with either therapeutic or adjunctive use with the surgery [165].

29.3.9 Bowen Disease

Bowen Disease (BD) refers to SCC in situ lesions of the non-genital regions which typically present as erythematous, well-circumscribed, irregularly bordered plaques. It mostly occurs on sun-exposed areas of elderly people with most common site being the head and neck. Well-known risk factors include UV radiation, arsenic exposure, radiotherapy, and immunosuppression [166]. It has also been postulated that human papillomavirus type 16 (HPV16) may be relevant with regard to development of BD on the hands and feet [167, 168]. Most studies identify the risk of the development of invasive SCC of about 3–5% [169, 170]. Diagnosis is mostly made by clinical evaluation with the aid of dermoscopy and sometimes, punch biopsy. Surgical excision although seems to be a simple, rapid and effective tool for treatment of the limited size lesions at favorable locations, cosmetic outcome and healing properties of the location should be thoroughly considered because of the multiple alternative non-surgical successful treatment modalities such as photodynamic therapy, 5-fluorouracil, imiquimod, radiotherapy, and laser [166].

29.3.10 Penile Intraepithelial Neoplasia

Penile intraepithelial neoplasia (PIN) term encompasses three distinct premalignant clinical entity of male genitals which all share identical histological features (SCC in situ) and may be mistakenly used interchangeably by physicians: (1) *Erythroplasia of Queyrat (EQ)* simply refers one or more red, moist, plaque sores of the mucosal surfaces of glans and inner surface of prepuce that almost always found in uncircumcised men. (2) *Penile Bowen disease (PBD)* presents as a single scaly plaque locating on the genital keratinized skin, mostly on the shaft. (3) *Bowenoid papulosis (BP)* consists of multiple, itchy, brown or pink-red, small papillomatous lesions on the penis (glans, prepuce, or shaft), groin, or perianal region that typically occur in younger and sexually active men [166, 171]. Some authors consider BP as a highly contagious sexually transmitted disease which also commonly associated with HPV16 [172]. Risk of malignant transformation seems to be more in EQ (approximately 10%) than PBD [173, 174]. Although BP usually resolves spontaneously, rarely it may undergo invasive SCC as well [175]. Important risk factors for PIN are as following: lack of circumcision, tobacco use, phimosis, HPV, chronic inflammation, and genital lichen sclerosis [166, 175]. Treatment can be challenging, especially in case of urethral involvement. Glansectomy, partial or total penectomy may be required for advanced lesions. Circumcision not only constitutes an important component of the treatment of the most of PIN lesions, but also prophylactically removes a major risk factor for invasive SCC and provides more abundant tissue for histologic evaluation [171, 174].

29.3.11 Genital Warts

Genital warts (GW, also known as condyloma acuminata) are clinical presentation of a sexually transmitted disease that mostly (approximately 90%) related to infection with HPV type 6 or 11. These two type HPVs are least likely to have a malignant neoplastic potential. GW usually presents as skin-colored, small (<5 mm) and exophytic lesions which can be found separately or in clusters in the anogenital area of the sexually active young individuals [176]. Typically, these lesions mostly regress spontaneously in 2 years. However, persistent lesions for many years bear significant risk for transforming into in situ *or invasive SCC,* especially in untreated lesions [177, 178]. *Buschke–Lowenstein* tumor refers to a rare, cauliflower-like giant condyloma of the perianal region that behaves locally invasive like a malignant lesion. Some authors consider these tumors to be benign lesions like GW, while others suggest these tumors to be malignant. Indeed,

some studies indicate 30–56% transformation rate of these lesions into invasive SCC [179, 180]. Despite the wide variety of treatment modalities, none of them are known to be efficient on eliminating HPV infectivity. Thus, primary goal of treatment should be ameliorating the symptom or removing the symptomatic lesion. "Gold-standard" treatment for *Buschke–Lowenstein* tumor is wide local excision with clear margins and, if present, complementary modalities according to histological invasion status [181]. Antiviral treatments such as interferon, immunomodulating agents, or imiquimod may be preferred rather surgical destruction or removal to eliminate surgical complications. However, surgery may still be treatment of choice because of the advantage of immediate results [182]. On the other hand, circumcision constitutes a prophylactic measure for prevention of the HPV transmission [178, 183].

29.3.12 Leukoplakia

Leukoplakia is the best-known lesion of the oral mucosa which bears malignant potential (Fig. 29.10). It can simply be defined as an oral mucosal white lesion that cannot be considered as any other definable lesion. Leukoplakia is thought to start as focal hyperkeratosis or hyperplasia progressing into some degree of dysplasia and ultimately carcinoma in situ or invasive oral SCC. Tobacco smoking, heavy alcohol consumption, betel nut chewing, and old age are the major risk factors [184]. Since it is a clinical term only, histopathologic evaluation is warranted to determine the severity of the lesion. Indeed, a clinical suspicion of leukoplakia diagnosis may end up with other conditions, such as candidiasis, bite keratosis, or lichen planus after histopathologic evaluation. There are several identified subtypes of oral leukoplakia, for example, homogenous, non-homogenous and proliferative verrucous leukoplakia, with malignant transformation risk varying between 1 and 10% per year and overall mortality rate up to 40% [184]. Biopsies indicating dysplasia or carcinoma in situ require surgical removal with clear margins, although recurrence may be up to 35%. A histopathological diagnosis of "hyperkeratosis with no dysplasia" or "keratosis of unknown significance" after excluding other benign conditions warrants special attention either for prophylactic complete removal or close follow-up with periodic biopsies depending on the size, multifocality, margin demarcation, and subtype of the leukoplakia [185].

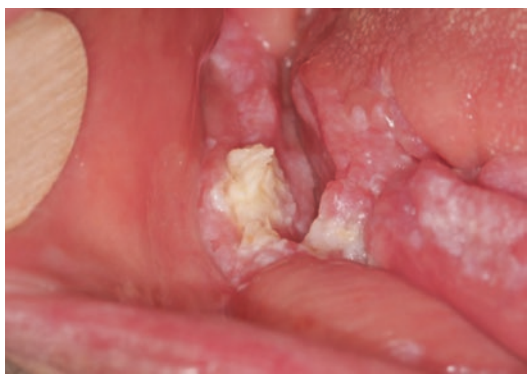

Fig. 29.10 Squamous cell carcinoma arising from leukoplakia of the right gingivobuccal groove

29.4 Cancer-Unrelated Conditions

As a shining new concept, prophylactic surgery is not only limited to cancer prevention but can also comprise wide variety of unwanted consequences or benign diseases that are intended to be prevented surgically. Accordingly, in addition to the cancer prevention, this book also aimed to review numerous cancer-unrelated and surgically preventable conditions in the specific organs and systems. However, plastic surgery is not generally confined to an organ or system and it mostly focuses on solving the "problem." Interestingly, dealing with the "problem" may conflict with the spirit of the prophylactic surgery whose fundamental purpose is to prevent the "problem." But it should be considered that solving a "problem," for example, repairing a cleft palate primarily aims to prevent more serious and irreversible "problem," such as speech abnormalities, as in this instance. While reviewing the surgical procedures from the top of the head to the tip of the toes involving patients ranging in age from new-

born to nonagenarian in the light of the prophylactic surgery perspective, we could identify less than a dozen conditions adaptable to the ideal description of the prophylactic surgery. We believe that these conditions ranging from basic to sophisticated are not limited to our appreciation and as the mentality of the prophylactic surgery expands and more widely adopted, the number of examples will increase both in number and diversity.

29.4.1 Fasciotomy/Escharotomy

A fasciotomy is a well-known and the only effective surgical treatment of the compartment syndrome (CS), which can be described as either an acute or a chronic condition, that is resulted from elevated pressure in a non-compliant osseofascial compartment. Elevated compartment pressure in turn gives rise to decreased circulatory pressure gradient between the vascular bed and tissues, and leads to ischemic necrosis of the muscles and nerves within the compartment. Surgical fasciotomy procedure typically starts with skin and subcutaneous tissue incisions and is followed by deep facial splitting along with the swollen fascial compartments (Fig. 29.11). However, an *escharotomy* normally does not include deep fascial plane [186]. It typically relaxes the full-thickness skin burns by superficial incisions, where the underlying structures are exposed to significant constrictive effect of the burned skin. If even a circumferential involvement is present, preventive value of the escharotomy rises in importance, because these constrictive forces sometimes can behave like a leather tourniquet and block the distal circulation or can lead a failure in thorax expansion for adequate ventilation [187–189]. However, concomitant injury of deep tissues after a full-thickness burn trauma can also cause inflammation, edema, and pressure increase within the fascial compartments. In such a case, fascial splitting in addition to escharotomy is mandatory in order to prevent CS.

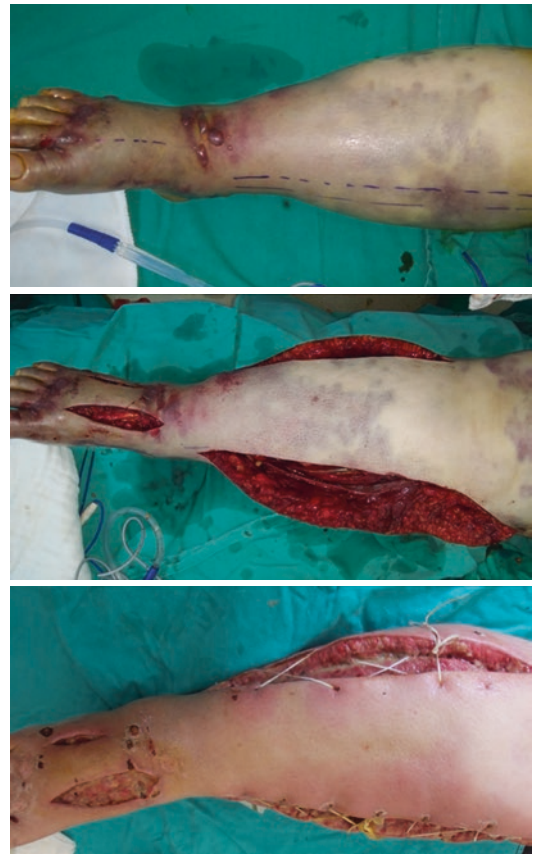

Fig. 29.11 Fasciotomy of a leg with a severe crush injury. The limb was salvaged without any ischemic sequela

Besides being a treatment modality, on the other hand, early fasciotomy can also be considerable as a complete surgical preventive measure if it is performed to alleviate increasing pressure of an injured compartment by timely recognizing the early signs of impending CS. Otherwise, late-diagnosed CS not only can cause devastating consequences, such as permanent functional damage or extremity loss, but also may end up with medico-legal litigations [190]. While as this makes CS of an important feared clinical condition for orthopedic and plastic surgeons, it also emphasizes the preventive importance of early fasciotomy or escharotomy procedures, which require experience, alertness, and well-directed decision-making.

29.4.2 Ectopic Implantation

Ectopic implantation or ectopic banking refers to a temporary and creative surgical solution for the amputated body parts that are unable to be readily replanted to where they anatomically belong to, because of an insufficient recipient site availability. Life-threatening concomitant traumas, hemodynamic instability or recipient site difficulties, such as gross contamination, massive tissue loss, or severe avulsion/crush injuries can cause a seek for a temporary adjourning of the primary replantation that can only be achieved by somehow ensuring the circulation of the amputated limb [191]. Marko Godina (1986) first described a case, in which an unperfused hand was initially implanted into the axilla via thoracodorsal vessels because of extensive damage and contamination of the recipient site and replanted back to forearm after appropriate wound care at postoperative day 66 [192]. Since then, many attempts of ectopic implantation of various organs such as digit, forearm, foot, scalp, penis, and testes have been published with up to 100% survival rate following secondary replantation [193]. However, the procedure still seems to be based on anecdotal data and has no consensus in terms of the indications, ideal banking location, banking duration, and technical considerations. Nonetheless, ectopic implantation constitutes a very important promising aspect of the plastic surgery which evidently can prevent limb loss and complex secondary reconstructive procedures.

29.4.3 Surgical Prevention of Lymphedema

Lymphedema of the arm is a well-known complication of the breast cancer surgery and effects approximately 20% of the patients who undergone breast cancer surgery [194], although the incidence highly varies depending on the breast/axillary surgery and adjuvant radiotherapy [195–197]. For example, while lumpectomy alone may only cause up to 3% of breast cancer-related lymphedema, it may reach up to 70% if modified radical mastectomy plus regional radiotherapy is implemented [198]. Clinical presentation is characterized by arm swelling due to disruption of lymphatic carriers and subsequent accumulation of the protein-rich fluid, and eventually progressive edema of the effected tissue. Arm swelling not only can cause significant disfigurement and decreased function but can also adversely affect the overall life quality [199–202]. Early physiotherapy [203, 204] and manual lymphatic drainage [205] are shown to be non-surgical preventive options with variable success for this debilitating condition. However, there are a couple of prophylactic surgical options available as well, all can be considerable as preventive measures for breast cancer-related lymphedema.

Sentinel lymph node biopsy (SLNB) is a well-known procedure for reducing the breast cancer-related lymphedema of the arm. This technique basically identifies the first lymph node (sentinel lymph node) draining the certain anatomic area just before draining to the subsequent regional nodes. Radionuclide injected near the tumor travels and accumulates in sentinel lymph node, which then located by surgeon with a specialized probe. Excision of the sentinel node(s) alone lets prevention of unnecessary removal of the remaining subsequent regional nodes and lymphatics if, for sure, the node comes free of tumor after histologic evaluation. SLNB has radically changed the approach in oncologic morbidity, especially in breast cancer. While the rate of lymphedema after axillary lymph node dissection has been estimated to range from 7 to 77%, SLNB procedure has decreased this range as low as 1–7% [194, 206–209].

Building on the similar principle of SLNB, Thompson et al. (2007) described another technique, *Axillary Reverse Mapping* (ARM), that identifies the lymph nodes draining the arm in a reverse fashion [210]. Herewith, they aimed to preserve arm lymph nodes by visualizing them intraoperatively, soon after injecting a dye into the medial arm that travels through the lymphatic channels towards to arm nodes of the axilla and colors the channels along with the nodes in the

meantime. A radionuclide injected from breast and a radiotracer consummate the ARM technique by allowing detection of cross-over lymph nodes (lymph nodes draining both the arm and breast), which are also recommended to be removed for oncological safety [211]. Multiple studies showed that sparing arm lymph nodes and excising the remaining lymph nodes of axilla has a significant reduced risk for lymphedema development [212–217]. However, anatomical variations [210, 213, 214], cross-over lymph nodes [218, 219], and increased arm lymph node involvement risk in patients with heavy nodal metastasis burden [220–222] have caused controversies about the oncological safety of this technique. Nevertheless, an ongoing prospective randomized controlled trial aimed to estimate the rates of lymphedema and regional recurrence will likely help making more accurate judgements [223].

The *Lymphatic Microsurgical Preventive Healing Approach* (LYMPHA) technique, described by Boccardo [224], uses microsurgical lymphaticovenous anastomosis after completion of axillary lymph node dissection to prevent lymphedema. Similar to ARM procedure, after injection of a dye from medial arm, colored afferent arm lymphatics are traced and divided just before they enter into the arm nodes. After axillary lymph node dissection is completed including the colored arm nodes, by performing a microsurgical technique, 2–4 of the divided lymphatics are anastomosed into a collateral branch of the axillary vein [224, 225]. By this technique they also reported 4% lymphedema rate with successful lymphaticovenous patency at 4-year follow-up [225]. In 2019, Ozmen et al. was also described an approach and named *simplified* LYMPHA (S-LYMPHA) in which the lymphaticovenous anastomosis is completed without using a surgical microscope [226].

29.4.4 Prophylactic Surgery for Wisdom Teeth

Wisdom teeth (third molars) usually erupt in between the ages of 17 and 24 years [227]. When

Fig. 29.12 Radiograph of an impacted left mandibular wisdom tooth

complete eruption into the normal functioning position of wisdom teeth is prevented despite a fully-grown root, impaction occurs. Lack of space, development in an abnormal position, or obstruction by another tooth are common reasons for impaction (Fig. 29.12) [228]. More than other teeth, wisdom teeth can fail to erupt or can erupt only partially, with a worldwide impaction prevalence of 24% [229]. While the impaction can usually present with several signs and symptoms, for example, painful, tender or swollen gums, bad breath and jaw pain, associated with the pathological conditions, such as caries, cysts, tumors, periodontal disease, pericoronitis and root resorption; a "disease-free" or "asymptomatic" impaction is called, however, if the patient does not experience any sign or symptoms that can be related to these pathological conditions [230]. When an impacted wisdom tooth resulted with a pathological change causing sign or symptoms of a local disease, clinicians and researches mostly agree on the surgical removal. However, on the other hand, regarding to knowledge indicating that this dentition plays no significant role in the oral cavity, extraction in the absence of an obvious pathological condition remains highly controversial among the global clinicians in dental surgery, researchers, and oral and maxillofacial surgeons [231–234]. Many systematic reviews have shown the lack of evidence to support or refute the prophylactic removal of the asymptomatic wisdom teeth [235–242]. The debate mostly centers on whether the health really needs such a surgical intervention bearing postoperative dis-

comfort and complication risks, as well as costs and economic burden. To clarify the arguments, it seems there is a need for research investigating the oral health-related quality of life, in the context of managing impacted wisdom teeth. However, aside from the arguments, current trends of the prophylactic removal tend to be practiced in a more individualized fashion based on clinical expertise, which involves case selection according to clinical and radiographic surveillance and patient-tailored risk assessments [242–245].

Impacted wisdom teeth are also focus of controversies resulted from their likely roles in the etiology of angle fractures, which constitute 16–35% of all mandible fractures [246, 247]. Systematic reviews showed the presence of mandibular third molars, possibly due to disruption of the cortical layer or occupation of bony space because of complete impaction, make the mandibular angle weaker and increases the fracture risk 3.7-fold [248, 249]. While several studies recommend the prophylactic removal of wisdom teeth to reduce the risk of possible angle fractures, especially in the athletes of contact sports [250–252], others disagree because the resultant increased strength in the angle region also increases the risk of condylar fracture, which has more serious complication potential [253–256].

29.4.5 Babysitter Procedure

Cross-facial nerve grafting (CFNG), first introduced in 1970s, is a method of importing motor axons from the unaffected side of the patient with unilateral facial paralysis that can be resulted from various conditions, such as head and neck cancer surgery, trauma, or radiotherapy [257–259]. In CFNG procedure, several cables of nerve grafts, interposed between the distal facial nerve branch of the unaffected side and the proximal facial nerve stump of the affected side, are aimed to convey regenerating axons from the unaffected contralateral facial nerve branches to the motor units of the paralyzed fascial musculature. Using the contralateral facial nerve and its nucleus as a motor source was not only an important breakthrough for coordinated muscle animation and emotional expression which could not be achieved by other sacrificed motor axon options (e.g., hypoglossal, accessory, trigeminal and phrenic nerves), but also was a worthwhile chance for avoiding the significant donor morbidities associated with these motor sources. However, since the regenerating axons normally proceed approximately only 1 mm/day and require a total of 8–12 months for reinnervation to begin, the relative long distance created by nerve grafts has been one of the important shortcomings of the CFNG procedure [260]. The elongated denervation of target fascial musculature and the risk of irreversible muscle atrophy limit the use of CFNG procedure unless it is performed within the 6 months from the onset of the facial nerve injury [260].

Babysitter procedure, introduced first by Terzis in 1984, aimed to overcome this limitation with two-stage surgical concept for facial reanimation [261, 262]. Although various modifications have been described since its inception [263–268], the procedure is simply performed as described [260]. In the first stage, as distinct from the routine CFNG procedure, following the coaptation of the proximal ends of the nerve grafts to the selected contralateral facial nerve branches, the distal ends are carefully secured in a labeled place in the affected side of the face. Then, a powerful motor donor nerve (masseteric or partial hypoglossal) coaptation is performed to the proximal nerve stump in the affected side with or without nerve grafts. This alternate motor source attached to the close proximity of the affected facial musculature prevent them from irreversible atrophy while awaiting appropriate, spontaneous and synchronous innervation through the nerve grafts from contralateral side. The second stage is performed after 8–12 months. This time, distal ends of the labeled nerve grafts filled with sprouting motor axons in the affected side are identified and coapted to the fascial nerve branches distal to the prior masseteric or partial hypoglossal nerve coaptation zone. While waiting the appropriately targeted, far *"mother"* reinnervation, prevention of irreversible atrophy of the fascial musculature by prompt reinnervation using a temporary motor

donor in the close proximity serve as *"babysitting"* and constitute a good example for a preventive surgical measure.

Successful preservation of the reinnervation capability of fascial musculature has also led the consideration of the use of babysitter procedure in peripheral nerve injuries [269–271]. Proximal ulnar nerve injuries are well-known with their poor motor functional return despite the proper repair because of the long distance regenerating axons must travel to reach denervated motor endplates [272]. In such injuries, anterior interosseous nerve can play a babysitting role as the masseteric or hypoglossal nerve does in the facial reanimation and prevent irreversible motor endplate changes until the regenerating axons arrive from the injury site above the elbow [273, 274].

29.4.6 Prophylactic Tendon Surgery

Tendon surgeries are mostly based on causation, such as repair of a torn or otherwise damaged tendon or restoration of the deficient functionality via transfer. However, there are also some other specific occasions in that prophylactic surgery can be relevant.

Rheumatoid arthritis (RA) is a chronic disease of unknown cause, which is characterized by progressive and systemic inflammation that shows a tendency to erode and destroy both articular cartilage and subchondral bone, thereby leading to functional limitations and disability [275]. Progressive damage involving wrist joints and synovial structures in the rheumatoid hand can increase the spontaneous rupture risk of the extensor tendons [276]. Symptoms of wrist tenosynovitis are obvious, including pain, swelling, and difficulty moving the affected joint. Spontaneous rupture, on the other hand, is characterized with sudden, painless inability to extend associated fingers. Several studies have shown that several pathologic signs on the imaging modalities can indicate an increased risk for spontaneous extensor tendon rupture risk [277–280]. Early recognition of these signs in patients with long-lasting tenosynovitis can suggest that these patients can benefit of prophylactic tenosynovectomy to prevent spontaneous extensor tendon rupture [281].

Extensor pollicis longus tendon (EPL), by the way, warrants special attention since its propensity for spontaneous rupture risk in some occasions that are not associated with RA. Mechanical factors, such as repetitive trauma resulting from a sharp bony edge (Lister tubercle or distal radius fracture) or the intrinsic bony anatomy of the third extensor compartment, as well as inflammatory etiologies, such as local/oral steroids or tenosynovitis so far have been hypothesized for the likely pathogenesis [282, 283]. However, there are also reports without any reasonable risk factors explaining the gradual weakening and the rupture of the EPL [284–289]. Some reports recommend prophylactic decompression of the contralateral EPL that presents with tendinopathy findings in case of spontaneous rupture of the other side [290, 291].

29.4.7 Prophylactic Surgery in Pressure Sores

As an almost complete preventable condition by non-surgical measures, pressure sores also have some prophylactic surgical procedures in the management. It is well-known that pressure sores mostly develop over the areas that have underlying bony prominences, such as trochanter, sacrum, ischial tuberosity, occiput, and heel. After first suggestion of removal of the underlying bony prominences as an adjunct to the surgical treatment of pressure sores [292], Arregui et al. (1965) reported "good" results in the 81% of 94 patients over a 10-year period who underwent total ischiectomy [293]. Subsequently, authors offered contralateral ischiectomy on a prophylactic basis since 28% of the patient with unilateral ischiectomy also developed contralateral ulcer. However, bilateral ischiectomy was later shown to be associated with high incidence of perineal ulcers and urethrocutaneous fistulas that resulted from

weight transfer to the pubic rami and perineum. Given the high incidence of these serious complications, total ischiectomy has been later recommended to be reserved for deep and recurrent ischial pressure sores [294, 295].

Resolving spasticity in patients who are prone to developing pressure ulcer may not only reduce the incidences but may also improve the life quality [296]. Besides the non-surgical therapies, surgical procedures such as local tenotomies, tendon transfers, rhizotomy, or myelotomy can be preferred for the prevention of the pressure sores associated with spastic malposition of the limbs [297–300].

29.4.8 Surgical Prevention of Diabetic Foot Ulcers

Diabetic foot ulcers (DFUs) are one of the most common and serious complications of diabetes and affect 15% of all diabetic patients [301]. While the lifetime risk to a person with diabetes for developing a foot ulcer could be as high as 25% [302], the individual recurrence rate could reach up to 70% after 5 years [303]. The primary factors in the development of these lesions are vascular insufficiency and peripheral neuropathy. Unperceived repetitive mechanical stress resulted from neuropathy is a major contributor in the development of the DFU, if especially the pedal pulses are also present. It is generally accepted that motor neuropathy-related foot deformities within diabetes usually occur as a combination of several pathologic scenarios. These scenarios involve atrophy of intrinsic foot muscles [304], stiffness of the flexor and extensor tendons leading to muscle imbalance [305], limited joint mobility caused by thickening of the ligaments and joint capsules [306], subluxations/dislocations, and gait abnormalities [304, 307]. As a result, these pathologic conditions lead to the structural foot deformities that are commonly reported as claw and hammer toes, prominent metatarsal heads, pes cavus, equinus deformity, and hallux valgus [304]. Various surgical techniques used for correcting these deformities, with only few exceptions, are primarily used in the context of ulcer treatment. However, because these interventions often change the structure, biomechanics, and pressure points of the foot, in addition to treating the DFU, they may have an enduring preventive effect for recurrences. One systematic review questioning the preventive effects of various surgical interventions that are normally preferred in correction of diabetic foot deformities and related DFUs found less recurrent ulceration risk in some techniques, such as Achilles tendon lengthening, single or pan metatarsal resection, and metatarsophalangeal joint arthroplasty when compared to the non-surgical treatment modalities. The authors also reported that procedures such as plantar fascia release and digital flexor tendon tenotomy may have promising value in preventing ulcer recurrence [308]. Well-designed controlled studies emphasizing the preventive importance of these procedures may lead to better understanding of their prophylactic potential.

The idea of the use of operative nerve decompression (surgical decompressing of nerves within the fibro-osseous tunnels in the leg) to treat clinical consequences of diabetic neuropathy in the lower extremity was first suggested over 30 years ago [309]. The pioneers of this approach advocated that diabetes mellitus-dependent metabolic effects may cause physical nerve enlargement leading to nerve trunk compressions in fibro-osseous tunnels of lower extremity, thereby causing local conduction blocks that can be attributable to the sensorimotor consequences of diabetic neuropathy. This has been followed by accumulating numerous clinical [310–318] and animal [319–323] studies testing the associated hypotheses: “symptoms of sensorimotor diabetic neuropathy may be due partly to compression of multiple peripheral nerves” and “surgical decompression of such nerves may result in symptomatic improvement.” Although studies mostly belong to limited number of research groups and have been criticized for the high bias risk, inappropriate designs, and

being scientifically "unproven" [308, 324, 325], plus despite the fact that the procedure has not been fully adopted, there are, indeed, many clinical studies indicating the success of nerve decompression not only in the symptomatic treatment of diabetic neuropathy [326] but also in the prevention of DFU recurrences [314, 317, 326–330].

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Prophylactic Cardiac and Vascular Surgery Procedures

30

Tahir Yağdı, Mustafa Özbaran, and Çağatay Engin

30.1 Introduction

Cardiovascular diseases are the leading causes of mortality, being responsible for approximately one-third of all deaths globally. Diseases concerning the field of cardiovascular surgery are mostly the coronary artery diseases, carotid artery diseases, valvular heart diseases, cardiac tumors, aortic aneurysms and peripheral arterial diseases. Patients may remain asymptomatic for a long period of time before the diagnosis. Thus, especially in the high-risk group of patients, periodical laboratory tests and further relevant interventions should be made in time, since a delay can lead to gradual deterioration of the patients. The two principal purposes of surgical therapy for this special patient population are: increase survival rates and improvement of the symptoms. This chapter provides a brief summary about the aforementioned diseases and the preventive surgical strategies, particularly in patients without symptoms.

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30.2 Coronary Artery Disease

Coronary artery disease, besides being one of the most important causes of mortality, is also one of the most frequently seen pathology in patients who undergo cardiac surgery. Risk factors such as older age, male gender, hypertension, diabetes mellitus, hypercholesterolemia, smoking, alcohol, obesity, unhealthy diet and nutrition, insufficient physical activity, family history and genetic predisposition and stress are commonly seen in patients with coronary artery disease.

Coronary artery disease is a serious condition which requires immediate treatment either by medically or surgically. In surgical point of view, the approach is to revascularization of the ischemic area. The principal goals of surgical revascularization for patients with coronary artery disease are to increase survival and to reduce symptoms [1, 2].

Coronary artery bypass grafting to improve survival is recommended for patients with more than 50% diameter stenosis of left main coronary artery [3]. Coronary artery bypass grafting to improve survival is also useful in patients having no symptom and with more than 70% diameter stenosis in three major coronary arteries or in the proximal left anterior descending artery with one of the other major coronary arteries (Fig. 30.1) [4]. Coronary artery bypass grafting also could be useful to increase survival in asymptomatic patients with significant stenosis in two major coronary arteries with severe or

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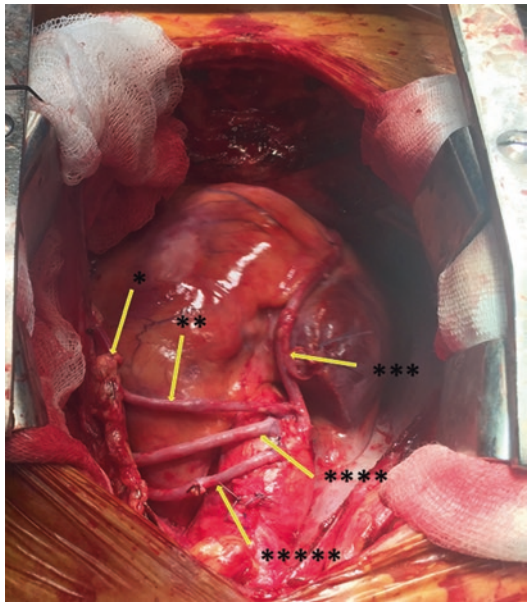

Fig. 30.1 Completed coronary artery bypass grafting operation performed with cardiopulmonary bypass via median sternotomy.*: LIMA graft to LAD; **: saphenous graft to D_1; ***: saphenous graft to RCA; ****: saphenous graft to OM_1; *****: saphenous graft to OM_2. (*LIMA* left internal mammary artery, *LAD* left anterior descending artery, D_1 first diagonal branch, OM_1 first obtuse marginal branch, OM_2 second obtuse marginal branch, *RCA* right coronary artery)

extensive myocardial ischemia or target coronary arteries supplying a sizeable region of viable myocardium [5].

30.3 Carotid Artery Diseases

30.3.1 Carotid Artery Stenosis

Carotid artery stenosis is well-known atherosclerotic process and is one of the main reasons of cerebrovascular accident. The asymptomatic carotid atherosclerosis study (ACAS) has confirmed that carotid endarterectomy is useful for the decrease of neurologic sequalae in patients with significant carotid stenosis from 18% to 7% over 5 years [6]. Numerous diagnostic tools exist for assessment of the disease, such as color Doppler ultrasonography, computed tomography angiography (CTA), magnetic resonance angiography (MRA) and intra-arterial digital

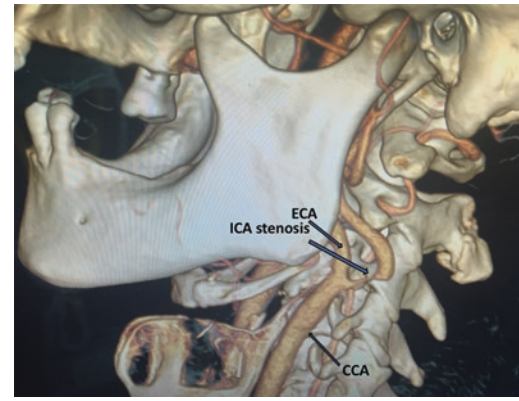

Fig. 30.2 3D reconstruction image of preocclusive carotid stenosis of internal carotid artery on CT angiographic examination (*CCA* common carotid artery, *ICA* internal carotid artery, *ECA* external carotid artery)

subtraction angiography (DSA). Precise estimation of the stenosis is usually made with CTA (Fig. 30.2).

Following the diagnosis, surgical removal of the atherosclerotic plaque is essential. Additionally, concomitant carotid artery endarterectomy in patients who undergo coronary artery bypass procedure is strongly recommended. Coronary artery bypass and carotid endarterectomy can be done either simultaneously or staged [7].

30.3.2 Carotid Body Tumors

Carotid body tumors are rarely seen clinical entities, which are generally located at the bifurcation of the common carotid artery as neuroendocrine neoplasms [8]. They are frequently located unilaterally and mostly have a benign nature. They can be seen both in men and women with equal proportions. Clinical presentation of the disease is variable. Approximately, two-third of the patients present with an asymptomatic mass on the neck, located alongside the sternocleidomastoid muscle. Since the process of progression is quite slow, patients often remain asymptomatic for a long period of time.

Vascular tumors originating from the chemoreceptor cells located at the carotid artery bifurcation are dense. Thus, surgical excision is considered as a potentially dangerous procedure.

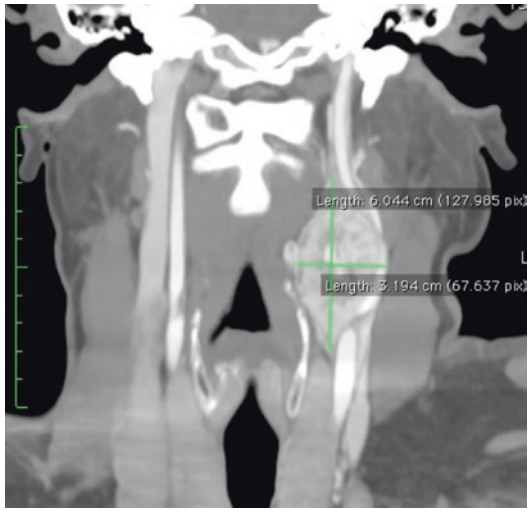

Fig. 30.3 Shamblin stage III carotid body tumor located at left carotid artery bifurcation

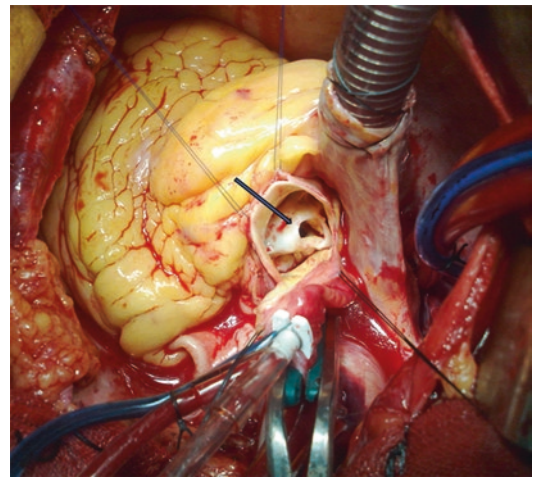

Fig. 30.4 Operative view of severe aortic stenosis

The proximity to cranial nerves (VII, IX, X, XI, XII) also causes a surgical challenge. Surgical categorization for carotid body tumors was suggested by Shamblin et al. [9]. Shamblin stage I tumors are rather small with insignificant invasion to the carotid artery. Surgical excision can be performed easily without disturbing the arterial structures. Stage II tumors are relatively bigger, but arterial adhesions can be separated. Shamblin stage III tumors are very big and more densely adherent to the vessels and nerves. These tumors usually need to be resected with arterial ligation and reconstruction. Most of tumors course asymptomatically in early stages. Diagnosis can be made with Duplex ultrasound scanning, CT angiography, MR angiography or carotid arteriography (Fig. 30.3). Surgery must be considered as soon as possible even in the asymptomatic patients to prevent the invasion of vascular and neural structures.

30.4 Valvular Heart Diseases

30.4.1 Aortic Valve Stenosis

The main etiologies for the condition of aortic stenosis are congenital, degenerative and rheumatic origins. The patients remain asymptomatic for a long period of time. Frequently seen symptoms are angina pectoris, syncope and congestive heart failure. When symptoms arise, there is a risk of sudden death. Around 50% of patients with severe aortic stenosis are asymptomatic when diagnosed. The decision of aortic valve replacement in such patients is still on debate [10, 11]. The degree of aortic valve calcification, appearance of symptoms, increase in the gradient and worsening of the left ventricular (LV) function should be observed closely. The goal must be the timely intervention of aortic valve replacement to preserve the cardiac function, stop additional damage and prevent mortality.

Asymptomatic patients with severe aortic stenosis and LV systolic dysfunction require operation [12, 13]. In asymptomatic patients with preserved LV systolic function, aortic valve replacement should be considered if there is another cardiac intervention planned. An early operation should be scheduled in case of aortic valve area of 0.75 cm^2 or an increase in transvalvular gradient during exercise (Fig. 30.4). Patients with coronary artery disease and moderate aortic stenosis with a mean transaortic gradient of more than 40 mmHg require combined procedures with coronary bypass and valve replacement [14].

Over the last decades, transcatheter aortic valve replacement has gained significant popularity, and the encouraging outcomes led the

increase of transcatheter procedures [15]. Despite developments, recommended technique for asymptomatic severe aortic stenosis is still the surgical aortic valve replacement.

Evaluation of whether the transcatheter aortic valve replacement should be done in patients with asymptomatic aortic stenosis, a prospective randomized controlled multicenter trial, was started in 2017. The evaluation of transcatheter aortic valve replacement compared to surveillance for patients with asymptomatic severe aortic stenosis (EARLY TAVR) trial evaluates whether there is benefit from transcatheter aortic valve replacement before patients become symptomatic (such as dyspnea, dizziness, fainting or angina pectoris). Similar studies may provide a direct guideline about the management of asymptomatic severe aortic stenosis.

30.4.2 Aortic Valve Regurgitation

Patients with aortic insufficiency are usually symptom-free for a long time. However, the increase in left ventricle diameter continues gradually as the disease progresses. In most patients, degree of aortic regurgitation increases slowly. In this way, it causes left ventricle to adapt the pressure changes by increasing its end-diastolic volume and resulting eccentric hypertrophy in the LV wall.

Progressive aortic insufficiency eventually results in ventricular dysfunction, cardiomegaly and decrease of LV ejection fraction. When patients become symptomatic, expected mortality would not be more than 4 years. Aortic valve replacement should be planned before the ventricular functions begin to deteriorate and decrease the ejection fraction.

According to AHA/ACC and ESC/EACTS guidelines, aortic valve replacement is recommended in asymptomatic patients with chronic severe regurgitation and LV ejection fraction less than 50% [12, 16].

Aortic valve replacement should be considered in asymptomatic patients with chronic severe regurgitation and LV ejection fraction greater than 50% in the presence of severe LV dilatation (LV end-systolic diameter >50 mm). Absence of symptoms with severe aortic regurgitation with normal LV systolic function and progressive severe LV dilation (LV end-diastolic diameter >65 mm) is another reasonable indication of surgery.

30.4.3 Mitral Valve Regurgitation

Mitral regurgitation is the most common valvular pathology in the North America and the second most common in Europe, necessitating surgical correction. It can be due to primary abnormalities of mitral valve (mitral annulus, anterior and posterior mitral valve leaflets, chorda tendinea) or secondary to LV dysfunction (functional or ischemic) (Fig. 30.5). Chronic mitral regurgitation causes LV enlargement and deterioration in the LV functions [17].

The severity of mitral valve pathology is estimated according to echocardiographic findings. Patients with severe, chronic mitral regurgitation may remain symptom-free for a long time. When compensatory mechanisms fail, symptoms of heart failure start to arise.

In patients with asymptomatic mitral regurgitation, on medical therapy, 5-year mortality is above 20% [18]. However, mitral valve surgery is associated with higher survival rates. In asymptomatic patients with preserved cardiac functions, severe mitral regurgitation will cause need

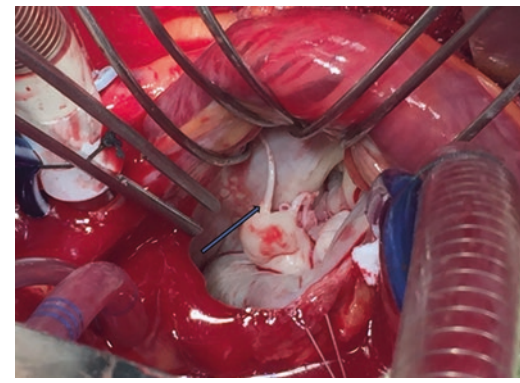

Fig. 30.5 Rupture of chorda tendinea is among common causes of mitral regurgitation

of a surgical intervention within less than 10 years.

Mitral valve surgery is indicated in asymptomatic patients with LV dysfunction (LV ejection fraction <60% and/or LV end-systolic dimension >40 mm). Mitral valve reconstruction is advised in asymptomatic patients with chronic severe primary mitral regurgitation due to flail leaflet and preserved LV systolic function, significant LA dilatation and presence of sinus rhythm.

In asymptomatic patients, mitral valve repair is reasonable if new onset atrial fibrillation or resting pulmonary hypertension exists (systolic pulmonary pressure at rest >50 mmHg) [13, 19]. Long-term survival of the patients treated with the nonsurgical approach was considerably lower compared with the group of patients who were treated with early surgical approach [20]. Especially in experienced hands, mitral valve repair has good success rates, with low-operative mortality. If the pathology is an isolated posterior mitral valve prolapse, success rates are even higher.

30.4.4 Mitral Valve Stenosis

The most common cause of mitral stenosis is acute rheumatic fever. Despite being less common, degenerative or congenital etiology is also seen.

In mitral valve stenosis, patients with moderate to severe stenosis (mitral valve area <1.5 cm^2) require for percutaneous or surgical therapy. Percutaneous mitral commissurotomy is considered as the appropriate choice in most symptomatic patients in the presence of appropriate anatomy. In asymptomatic patients, surgery is restricted to those at higher risk for cardiac complications (systemic embolism or hemodynamic decompensation) who have contraindications for percutaneous mitral commissurotomy (i.e., left atrial thrombus) and to those having low risk for surgery. For the most part, surgical method is the replacement of the mitral valve.

30.4.5 Tricuspid Valve Regurgitation

Tricuspid regurgitation is mostly seen as a secondary to right ventricular dysfunction with increased volume and pressure load. Besides, left-sided pathologies can also cause tricuspid regurgitation by putting pressure loads on the right side of the heart, leading to the right ventricular and tricuspid annular dilatation. Increased right atrial pressures may cause hepatic congestion, ascites and pretibial edema. Most of the conditions, leaflets of the valve are anatomically normal [21].

The timing of the surgical intervention is critical. In severe primary tricuspid regurgitation, if the progressive right ventricular enlargement or deterioration of the right ventricular function is detected, surgical intervention should be carried out in asymptomatic patients. A delay in surgical timing may cause permanent right ventricular dysfunctions, leading to suboptimal surgical outcomes. As a surgical technique, tricuspid valve repair with ring annuloplasty is considered superior to valve replacement (Fig. 30.6) [22].

30.4.6 Tricuspid Valve Stenosis

Among other valvular pathologies, tricuspid stenosis is rarely seen. Most of the time, it is accompanied by another mitral valve disorder,

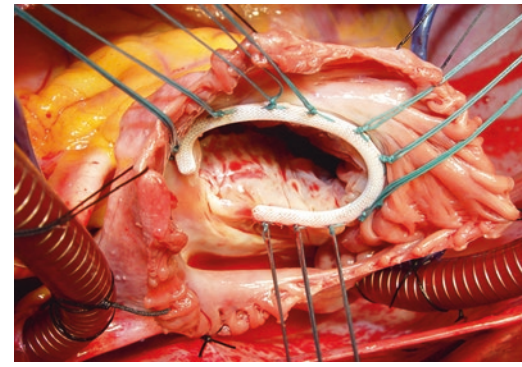

Fig. 30.6 Tricuspid ring annuloplasty for severe tricuspid regurgitation

particularly in patients with rheumatic heart disease. Some other etiologic factors are congenital, right atrial tumors, endomyocardial fibrosis and carcinoid syndrome [23].

30.5 Cardiac Tumors

Cardiac tumors can be seen either primarily or secondarily. Primary cardiac tumors are classified as benign and malignant tumors. Approximately, 3/4 of primary tumors are benign. Almost half of the benign tumors are atrial myxomas, and about 75% of the malignant tumors are sarcomas [24]. The most common primary tumor in children is known as the rhabdomyosarcoma.

30.5.1 Myxoma

Myxoma is the most common primary cardiac tumor in adults. Most of them originates from the left atrium, secondly from the right atrium [25]. Most popular clinical pictures are intracardiac obstruction (mostly mitral orifice) with congestive heart failure, peripheral embolization, fever, fatigue or weight loss [26]. Surgical resection is the only effective option for patients with cardiac myxoma and should be accomplished as soon as possible before deadly complications occur (Fig. 30.7).

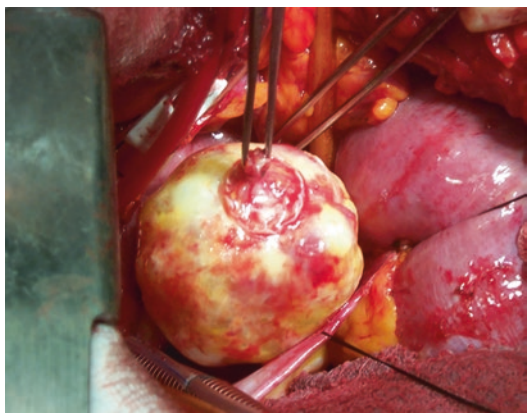

Fig. 30.7 Surgical excision of huge left atrial myxoma

In few patients, myxoma can be diagnosed incidentally on routine echocardiography without any symptoms and signs associated with it. The medical history may not reveal any event of cerebrovascular infarct, syncope or shortness of breath, suggestive of obstruction or embolism. It is realistic to decide an urgent surgery in asymptomatic atrial myxoma. During the operation, careful attention should be made to avoid manipulation of the heart to prevent arise emboli from myxoma. The tumor should be excised completely. Most of the patients continue living their normal lives without symptoms. Despite the recurrence very rare, repeated echocardiographic evaluation is useful to detect development of a repeated myxoma.

30.5.2 Papillary Fibroelastoma

Papillary fibroelastoma of the heart valve is the second most common cardiac tumor (approximately <10% of all), which is usually diagnosed in postmortem examination. With the increased use of echocardiography, papillary fibroelastoma can be diagnosed incidentally on routine cardiac examination. Despite the benign nature, high incidence of systemic embolization and obstructive complications (i.e., coronary ostial complications) warrants surgical resection in large tumors [27].

30.5.3 Rhabdomyoma

Rhabdomyoma is the most common cardiac tumor in children and often seen in newborn. More than half of the cases are associated with tuberous sclerosis. It can be located in both of the ventricles and often tends to be multiple [28]. Obstruction of valvular orifice or intraventricular chamber and resulting heart failure is the main, most common complication. If patient is asymptomatic and is not diagnosed with tuberous sclerosis, prompt surgical intervention must be applied during the first year of life. When symptoms arise, it can be understood that the tumor is

usually disseminated, and the rate of surgical success is unfortunately very low.

30.6 Other Cardiac Diseases

30.6.1 Cardiac Hydatid Cyst

Hydatid cyst is an endemic parasitic infection, typically seen in rural areas. However, parasitic infection of the cardiac structures by *Echinococcus granulosus* is not common [29]. The diagnosis can be challenging, since the signs can be unpredictable. The clinical course can vary from asymptomatic to sudden death, depending on the part of the affected body and the dimension of the cyst. First rule of the diagnosis is to anticipate the cardiac hydatidosis, especially in endemic regions. The mostly involved part of the heart is the LV myocardium [30].

It can be diagnosed incidentally by routine diagnostic tools, such as chest X-ray, ECG, echocardiography or computed tomography. The most recommended treatment of cardiac hydatid cyst is total excision and plication of cyst cavity (Fig. 30.8). Surgical intervention should be performed, including asymptomatic patients, as soon as possible, since the follow up with medical therapy cannot prevent rupture of the cyst and its catastrophic complications (rupture, tamponade, systemic anaphylaxis, embolization, low cardiac output syndrome).

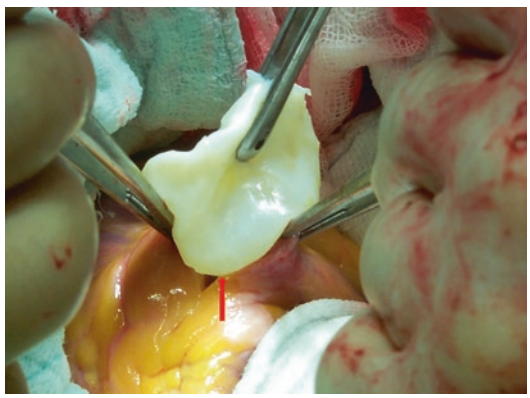

Fig. 30.8 Surgical removal of left ventricular hydatid cyst

30.7 Aortic Diseases

30.7.1 Aortic Dissection

Basic definition of aortic dissection, mainly due to hypertension and aortic wall structural anomalies, is the separation of tunica media from tunica intima caused by a tear in the aortic wall and misdirection of blood flow toward the tear. Natural course of the disease depends on the localization. For Stanford type B aortic dissections, which start from the aortic zone distal to the left subclavian artery, surgery is limited to certain circumstances, such as malperfusion, acute dilatation and rupture; whereas, Stanford type A aortic dissection, which starts from the ascending aorta, always requires an emergent operation [31]. Dissections involving ascending aorta are at high risk for rupture, cardiac tamponade, acute aortic valve insufficiency, acute myocardial infarction and malperfusion when left unoperated. Indicatively, half of these patients die within the first 48 h and 80% in the first week [32]. Patients usually present with acute severe chest pain or back pain, and sometimes the symptoms of malperfusion, can be present. Rarely, the patients may remain asymptomatic, surviving the acute phase, which lead to chronic aortic dissection and related aneurysms. Surgery should be performed, especially aneurysms with increased diameters to prevent rupture, and eventually, the death.

30.7.2 Proximal Aortic Aneurysms

Some pathologies of the proximal aorta can have an asymptomatic clinical course. Among these, main group includes aneurysms of the ascending aorta and arcus aorta. Majority has a silent course, which results in sudden death due to rupture and cardiac tamponade. The most important factor for prediction of the rupture risk is the diameter of the aneurysm. Rupture risk begins when diameter reaches 5 cm and above. It becomes apparent with the diameters over 5.5–6 cm and above [33].

Chronic obstructive pulmonary disease, smoking, uncontrolled hypertension, renal failure and

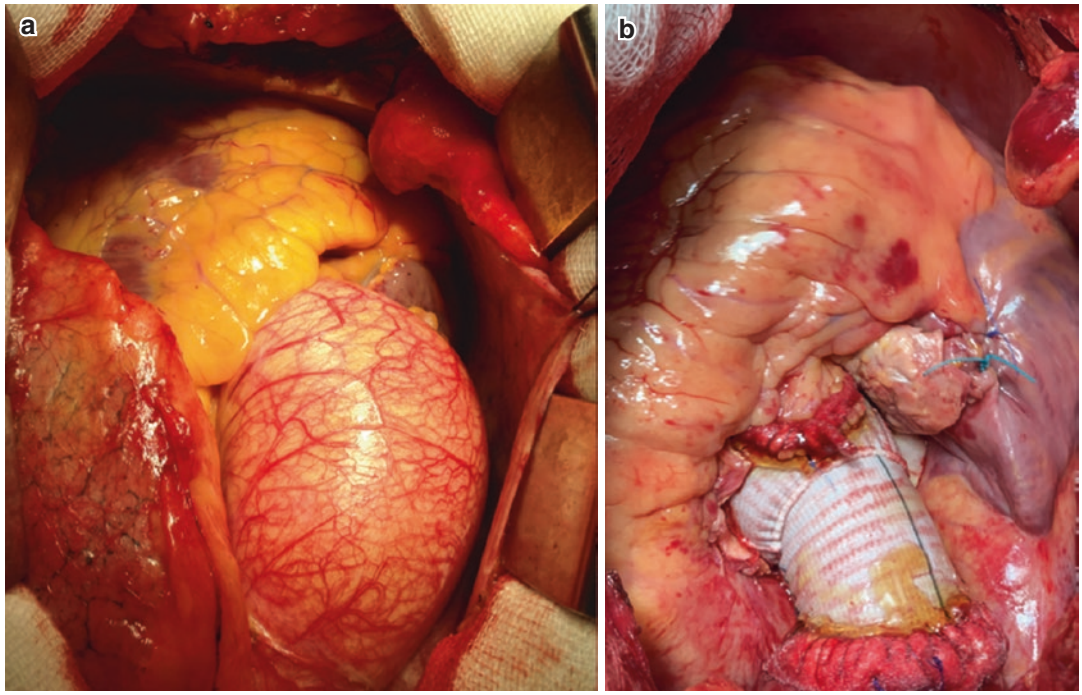

Fig. 30.9 (**a**) Operative views of ascending aortic aneurysm. (**b**) Surgical repair of ascending aortic aneurysm with Dacron graft and coronary ostial implantation

aortic structural diseases (i.e., Marfan syndrome) are the other risk factors for rupture [34].

Patients may experience chest pain or dyspnea due to concomitant aortic valve pathologies or may remain asymptomatic. Patients should be followed up according to the ascending aortic diameter, which when reaches to certain levels, should be operated immediately to prevent rupture, even an asymptomatic clinical course is present. The current gold standard treatment for ascending aorta and arcus pathologies is the open surgical approach (Fig. 30.9a, b). However, there are limited series studies with endovascular techniques.

30.7.3 Distal Aortic Aneurysms

Thoracoabdominal aortic aneurysms form an important part of distal aortic aneurysms. These pathologies are complex and challenging for surgeons. These patients tend to have multiple risk factors, operative mortality and morbidity.

These aneurysms may originate anywhere in the descending aorta distal to the left subclavian artery and involve different levels of abdominal. From surgical point of view, it may be necessary to open both thorax and abdomen (Fig. 30.10). As the aneurysm involves more structures on different levels of the aorta, more intercostal, lumbar and visceral branches arise from the aneurysm, and duration of operation extends, risking of ischemic injury of relevant tissue and organs.

While investigating natural course of distal aortic aneurysms, it is shown that 2-year survival rate of the patients who are treated medically was only at 24% [35]. These are the patients who were followed up with medical treatment due to various impediments for the surgery. Mostly, the patients die from the rupture of the aneurysm sac and hemorrhagic shock that follows. In a recent trial, critical threshold for rupture was found to be 6 cm for thoracoabdominal aortic aneurysms and 6.5 cm for descending aortic aneurysms. However, dissection may occur in smaller diameters [36].

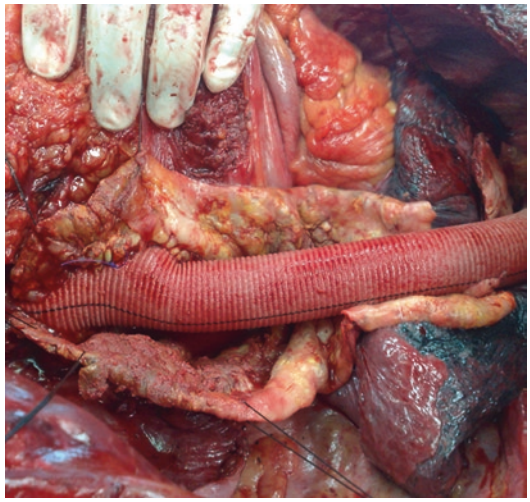

Fig. 30.10 Thoracoabdominal aortic aneurysm repair via thoracoabdominal incision

Abdominal aortic aneurysms are the most common type of aortic aneurysms. For asymptomatic patients, surgical repair is the standard approach to prevent rupture. Elective abdominal aortic surgery is recommended when the risk of rupture exceeds the risk of surgical intervention. Generally, the risk of aneurysm rupture surpasses the risk related with surgical repair when aneurysm diameter becomes 5.5 cm and above. Surgical repair of asymptomatic abdominal aortic aneurysm is frequently indicated when diameter exceeds 5.5 cm [37]. Currently, there are two techniques for abdominal aortic aneurysm repair. These are open repair and the abdominal endovascular aneurysm repair (EVAR) (Fig. 30.11).

Similar to type B dissections and descending aortic aneurysms, endovascular repair superseded open surgery in abdominal aortic aneurysms. Randomized trials showed the EVAR superiority over open surgery, especially in the early outcomes. Furthermore, blood loss, cardiopulmonary complication rates, hospital stay and periprocedural risk are lower with EVAR technique than open surgery [38]. However, there is no difference for long-term complications, long-term survival rates between EVAR and open surgical approach [39].

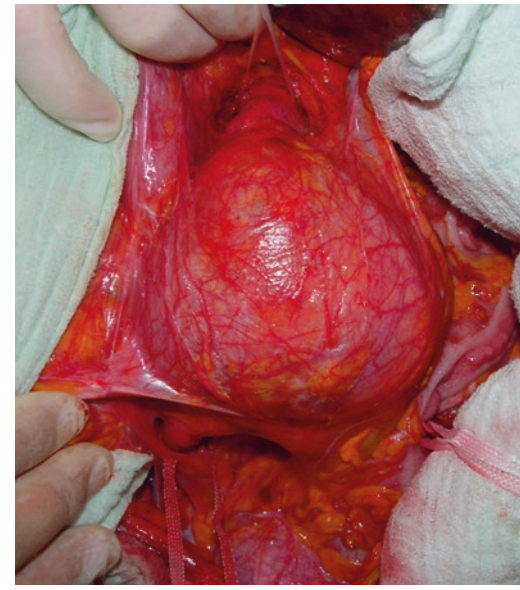

Fig. 30.11 Operative view of abdominal aortic aneurysm

30.7.4 Femoral and Popliteal Artery Aneurysm

Femoral aneurysms are usually pseudoaneurysms, whereas the popliteal aneurysms are generally degenerative true aneurysms. The femoropopliteal aneurysm should be investigated in patients with aneurysm in the aortoiliac segment. The association of femoral aneurysm with abdominal aneurysms has been reported as 50–90%, and in popliteal aneurysm around 30–50%. Femoral true aneurysms are generally having an asymptomatic clinical course. As the aneurysm sac grows, the symptoms may arise. Leg ischemia due to embolism and symptoms of compression can be seen. Obstructive symptoms, including compression of the nerves, adjacent venous obstruction and thromboembolism, can induce ischemic symptoms. Large and thrombus-containing asymptomatic popliteal and femoral aneurysms should be treated surgically or interventionally to prevent further ischemic complications.

30.7.5 Popliteal Entrapment Syndrome

Popliteal entrapment syndrome involves an abnormal relationship between the popliteal artery and the medial head of the gastrocnemius muscle [40]. The sudden onset of symptoms is more commonly seen than slow progressing claudication. Symptoms usually can arise as a result of a heavy exercise. Some patients remain asymptomatic until an acute occlusion of the popliteal artery develops or until thromboembolic complications arise due to post-stenotic dilatation. Muscle resection and relief the decompression of the popliteal artery provides the necessary healing.

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Prophylactic Chest Surgery Procedures

31

İrfan Yalçınkaya and Mahmut Talha Doğruyol

31.1 Introduction

Prophylactic surgery is generally used to describe the process of minimizing the risk of cancer by surgically removing a tissue or organ with the potential to develop a tumor. Thus, the surgical intervention to benign or premalignant lesions with the potential to develop malignancy or excision of a pathological structure before it gets complicated also falls into this category. Prophylactic surgery, commonly used for hereditary breast or ovarian cancer, is not an unfamiliar definition for thoracic surgery. This surgery option has been used for many years in bulla with the potential to complicate into a pneumothorax or tuberculosis sequelae, which may become complicated. The list can be further expanded with congenital malformations or excision of a premalignant lesion with the potential to develop malignancy within the thorax. The present study aimed to discuss the prophylactic surgical procedures regarding chest surgery. Prophylactic surgical procedures in the field of chest surgery can be classified into two categories: benign pathologies and precancerous pathologies.

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31.2 Benign Pathologies

In general, the morbidity and mortality of an elective surgical procedure are always lower than those of emergency surgery. Therefore, surgical interventions, planned for pathologies likely to be complicated, have been generally accepted among thoracic surgeons, as these interventions can be lifesaving. The prophylactic surgery indications for benign pathologies that are reported in the literature are mentioned under this title. Thus, prophylactic surgery application is reported in several special benign conditions.

31.2.1 Pneumothorax

Surgery is indicated if a complication, such as prolonged air leak or hemothorax, develops in the first episode of pneumothorax. However, occupational risks, such as aircraft personnel or divers, being in isolated areas away from medical institutions, and psychological reasons, indicate prophylactic surgery [1]. If no surgery is performed, the chance of recurrence is up to 75% within 5 years after the first episode; however, this rate increases to 83% after the second episode [1, 2]. It is reported in the literature that 10–20% recurrence is possible in those who undergo only

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bullectomy [3]. These high risks of recurrence have prompted thoracic surgeons to investigate which factors are decisive for the development of recurrence in pneumothorax. The presence of bullae on high-resolution computed tomography (HRCT) for pediatric patients presenting with pneumothorax has been reported as a risk factor for ipsilateral recurrence. Studies show that prophylactic surgery can be performed in these patients [4, 5]. Contralateral bullae visible on HRCT and a low body mass index have been reported as the indications for prophylactic surgery in adult patients with pneumothorax (Fig. 31.1) [6, 7].

Sihoe et al. [8] emphasized the importance of preoperatively performed computed tomography (CT) imaging of patients with primary spontaneous pneumothorax. They reported contralateral bullae or blebs in 53.6% of patients; contralateral pneumothorax developed in 26.7% of them during the follow-up period. Besides, none of the patients with contralateral bullae or blebs developed contralateral pneumothorax during the follow-up. For this reason, it was stated that prophylactic treatment could be performed in the presence of contralateral bullae or blebs on CT in patients with primary spontaneous pneumothorax [8]. Liu et al. [9] reported that 70 of 335 patients with primary spontaneous pneumothorax, who showed contralateral bullae or blebs, underwent bilateral video-assisted thoracoscopic surgery (VATS) in a single session. The recurrence rate in the VATS group was low, and hence the necessity of prophylactic treatment in these patients was emphasized. This surgery would reduce hospital stays and relieve patients of

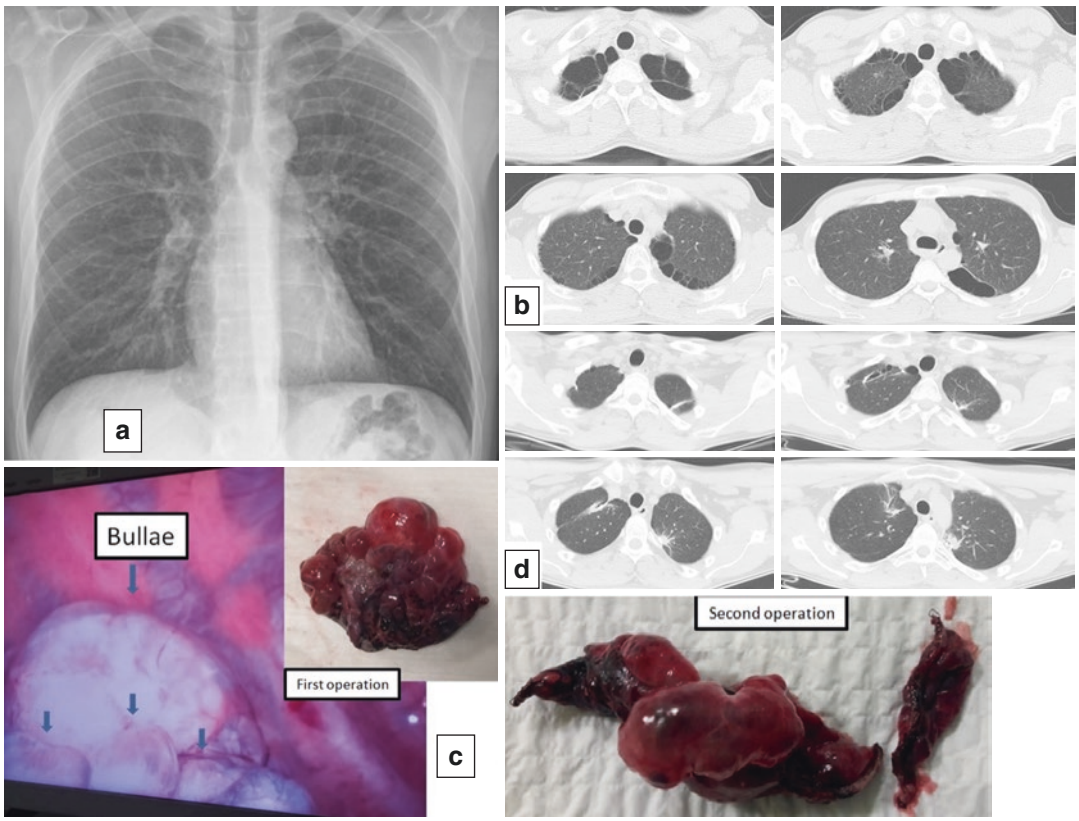

Fig. 31.1 (**a**, **b**) Bilateral bullae are seen in chest X-ray and axial computed tomography images of a young, smoker, asthenic, male patient scheduled for prophylactic surgery, (**c**) video-assisted thoracoscopic surgery with wedge resection and pleural abrasion was performed in two separate sessions, first on the right and then on the left, in one and a half months intervals, (**d**) postoperative control axial computed tomography

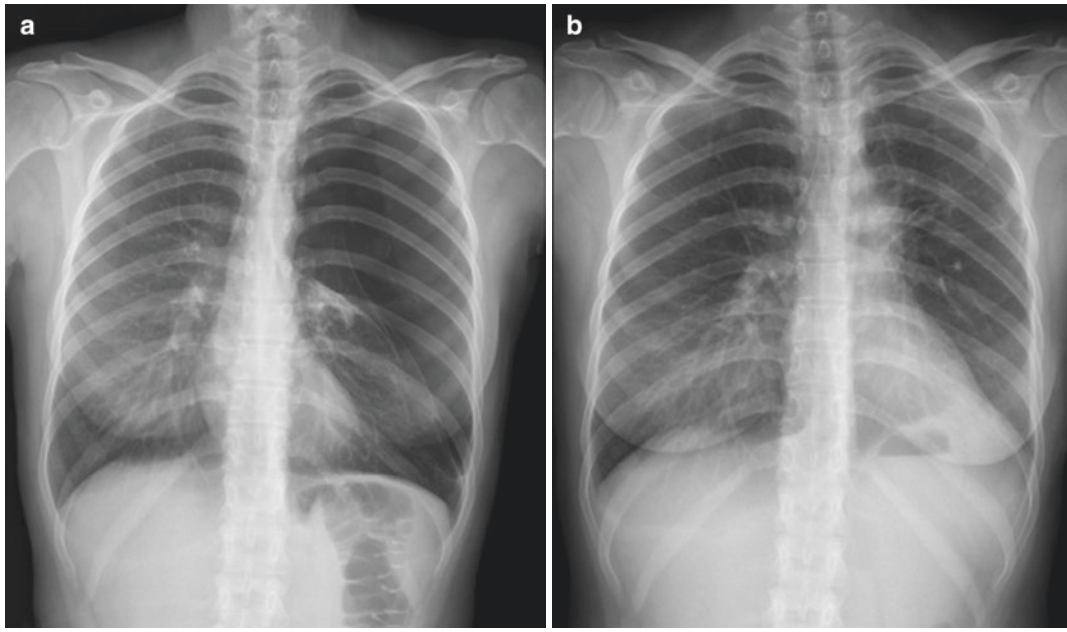

Fig. 31.2 (**a**) A giant bulla is seen in the preoperative chest X-ray of a young female patient, (**b**) postoperative chest X-ray of the same patient shows re-expansion of the lung

potential socioeconomic and psychological burdens [9].

However, Li et al. [10] performed preventive surgery in both hemithoraces with a single incision in 18 patients with primary spontaneous pneumothorax diagnosed with contralateral blebs. Patients who were not intubated and had received mask and epidural anesthesia underwent ipsilateral surgery via an incision through the fifth or sixth intercostal space on one side while lying in a semi-supine position. Contralateral prophylactic surgery was performed in the same session, passing from the anterior mediastinum to the hemithorax. This method was found to be safe and feasible [10].

31.2.2 Giant Bulla

The presence of a giant bulla, the development of pneumothorax, or the patient showing symptoms are general indications for surgery. However, asymptomatic patients should only be considered for prophylactic surgery when the bulla fills one-third of the thoracic cavity because severe and irreversible complications may develop in such patients (Fig. 31.2) [1, 11]. It is better to operate these patients using minimally invasive surgical options to reduce postoperative pain and improve cosmetic outcome if possible (Fig. 31.3).

Also, as the compression time of a giant bulla on the intact lung parenchyma increases, parenchyma's function is less likely to return to normal even if the lung is fully expanded. The possible reasons for this are the loss of surfactant in the parenchyma without function and the development of varying degrees of interstitial fibrosis [11].

31.2.3 Tuberculosis Sequelae

Tuberculosis sequelae develop due to either the damage caused by the disease in the lung parenchyma or collapse treatment. Lung lesions appear as bronchiectasis, fibrostenosis, and cavitation, while lymph nodes are characterized by bronchiolitis. Aspergilloma can develop in these lesions in the parenchymal cavity, or chronic suppurative disease can lead to damaged lungs, making the situation more complicated [12].

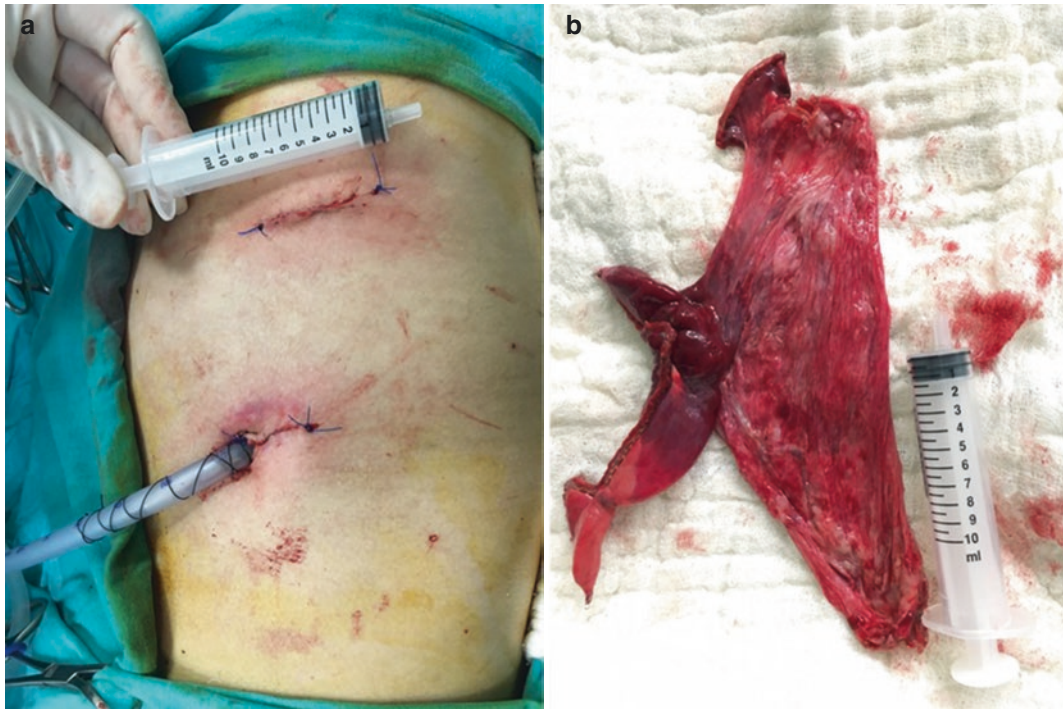

Fig. 31.3 (**a**) Video thoracoscopic incisions of the patient mentioned in Fig. 31.2, (**b**) pathological specimen image of the same patient

Surgical indications can only be mentioned if symptoms develop in the tuberculosis sequelae. In asymptomatic patients, prophylactic surgery should be considered only in the presence of aspergilloma. Planned prophylactic surgery in asymptomatic patients with aspergilloma significantly reduces morbidity and mortality. In contrast, emergency surgery of patients with symptoms of acute hemoptysis increases these. Careful hilar dissection for maintaining bronchial blood flow when performing anatomical resection and careful hemostasis to prevent postoperative bleeding is essential. Covering the bronchial stump with supporting tissue is vital to avoid fistula development if pneumonectomy is performed [13].

31.2.4 Pulmonary Arteriovenous Malformations

Congenital vascular pathologies may originate from the pulmonary artery, pulmonary vein, or lymphatic vascular system. Most of these anomalies are diagnosed early in life as cardiac malformations and severe cardiorespiratory symptoms accompany them. However, a small group of patients is not diagnosed until adulthood or may be asymptomatic [14].

Pulmonary arteriovenous malformations (PAVMs) are characterized by abnormal junctions between the pulmonary artery and the vein; their most common cause is Osler–Weber–Rendu disease (hereditary hemorrhagic telangiectasia). Most of these patients are diagnosed as they show symptoms. Only a tiny patient population may be asymptomatic, or the patient may have been diagnosed and is being followed up. Spontaneous arteriovenous fistula-induced bleeding may occur in these patients. Iwabuchi et al. reported a case in which emergency thoracotomy was performed due to the spontaneous development of intrathoracic hemorrhage in an asymptomatic patient with PAVM followed up for 5 years and recommended prophylactic surgery, especially in peripheral lesions under the visceral pleura [15]. In recent years, arterial

embolization has also been frequently used to treat these patients [14].

31.2.5 Sequestration

These intrathoracic lesions, which feed from the systemic circulation and have no contribution to breathing, are divided into two groups: intrapulmonary and extrapulmonary. Prophylactic surgery is recommended for both types because of the risk of infection, whereas the risk is higher in intrapulmonary lesions [16]. A prophylactic surgical indication is also mentioned due to the risk of malignant degeneration in both intrapulmonary and extrapulmonary sequestrations [17].

31.2.6 Diaphragmatic Paralysis

A prophylactic plication of the diaphragm can be performed when phrenic nerve injury develops in patients undergoing thoracic surgery, or to reduce future respiratory complications due to a tumor invading the phrenic nerve during the same session. The results of the prophylactic plication of the phrenic nerve were investigated in the best evidence topic article that examined a total of 4 studies with 37 patients plus 2 animal studies. It is reported that plication with phrenic nerve injury reduced the postoperative radiological diaphragmatic paralysis image, the shortness of breath, and the need for a ventilator. The predicted values of the respiratory function of patients who underwent lung resection and diaphragmatic plication in the same session were consistent with the measured postoperative values. The authors concluded that a diaphragmatic plication could be performed during surgery if the phrenic nerve was injured or sacrificed [18]. In the extended resection study of Tokunaga et al. [19] conducted with 13 patients, one of the studies examined in the aforementioned best evidence topic article, postoperative complications did not develop in 77% of patients. Further, it was emphasized that no diaphragmatic paralysis occurred clinically or radiologically in any patient during the postoperative period [19]. Takahashi et al. (2018) reported a case in which the patient underwent left upper lobectomy and plication with VATS because the left upper lobe lung cancer invaded the phrenic nerve [20].

The situation is similar in cases with pneumonectomy. Another best evidence topic article that examined four studies reported that the plication of the hemidiaphragm due to the development of paralysis after pneumonectomy reduced respiratory failure. This result was because a preserved phrenic nerve after pneumonectomy can function for up to 11 years, and plication mimics such a function [21].

31.3 Precancerous Pathologies

One of the main topics related to thoracic surgery in terms of malignancy is lung cancer. Although genetic predisposition is involved in lung cancer development, tobacco use is the most common etiological cause of lung cancer [22]. Other etiological factors, such as passive smoking, air pollution, workplace exposure, and genetic sensitivity, should not be ignored. In recent years, an individual who has never smoked in his life is thought to have an increased tendency to have lung cancer. Adenocarcinomas mostly occur in these individuals. These tumors contain mutations more prone to targeted therapy compared with lung cancer in smokers [23].

We can easily make an inference with today's knowledge that no hereditay tumor in thoracic surgery is suitable for prophylactic surgery for reasons, such as the lung being a vital organ, very small genetic predisposition in the tumor's etiology, and not knowing in which part of the lung the tumor may develop, even if it is predicted. However, prophylactic surgical indications can be counted in benign or premalignant lesions of almost all thoracic structures, including lung parenchyma.

31.3.1 Benign Chest Wall Tumors

The only prophylactic surgical indications for benign chest wall tumors are for osteochondroma

and chondroma. Unlike other benign ribcage tumors, these tumors have a risk of malignant degeneration. Osteochondroma is a small, slow-growing tumor. The risk of malignant degeneration after surgery is eliminated, and recurrence has not been reported [24]. It may be challenging to distinguish chondromas from early-grade chondrosarcoma, even under a microscope. Therefore, resection with a minimum of a 2 cm surgical margin is recommended at the time of diagnosis [25].

31.3.2 Benign Pleural Tumors

Although solitary fibrous tumors are benign, they should be treated surgically after diagnosis because of the risk of developing Doege–Potter syndrome (which may be fatal), the possibility of malignant transformation, and the potential of rapid growth after many years of follow-up [26–28]. Surgical margins should be observed during resection, and patients should be followed up by CT for many years to prevent recurrence [29, 30].

A condition called reactive mesothelial hyperplasia with recurrent pleural effusion has been described in the literature [31]. In people with asbestos exposure, in situ mesothelial lesions, which are considered as the precursor of mesothelioma, have also been shown. Malignant pleural and peritoneal mesotheliomas have been reported in a patient diagnosed with atypical mesothelial hyperplasia 8 years later [32]. Histologically important characteristics, degree of mesothelial proliferation, superficial invasion, uniform mild cytological atypia, and mesothelial proliferation reasons other than asbestos have been put forward for patients with atypical mesothelial hyperplasia. However, no information is available on whether to perform preventive decortication in patients with these characteristics and how it affects the process.

Also, pleura-induced thymomas, well-differentiated papillary mesotheliomas, and desmoid tumors with low malignancy potential can be treated with prophylactic surgery after diagnosis [33].

31.3.3 Congenital Lung Malformations

Severe respiratory distress develops in most patients with congenital pulmonary airway malformation (CPAM). However, a small portion of patients may remain asymptomatic. Although surgery is undeniable for symptomatic patients, no consensus exists on whether to perform prophylactic surgery in asymptomatic ones [34].

Hsu et al. (2019) examined the development of cancer gene mutation in patients with CPAM and reported that these patients carried a higher risk than the healthy population, and prophylactic surgery might be an option [35]. Malignant transformation is not uncommon in asymptomatic patients, and malignancy may develop even after many follow-ups [36]. Thus, it was emphasized that aggressive prophylactic surgery is acceptable, and low morbidity prevails over the risk of malignancy [37]. In a study in which parenchymal prophylactic surgery (segmentectomy or atypical resection) was performed in 50 patients, prophylactic sublobar resection was suggested to be performed within the first 6 months, if possible, with VATS, in asymptomatic patients [38]. Similarly, Moyer et al. (2017) reported that prophylactic surgery might be performed with VATS within the first 6 months of life or later due to the risk of malignancy and infection development [39]. Another study reported that prophylactic surgery for congenital lung cysts did not prevent the development of pleuropulmonary blastoma. However, resection was still suggested in all pediatric patients with lung cysts due to the presence of risk [40].

Opposing views exist for prophylactic surgery in patients with CPAM. Two patients with right lung agenesis, aged 44 days and 3 months, were approached with the conservative treatment method; aggressive surgical intervention was avoided. Both patients responded very well to the conservative treatment method. These studies emphasized that prophylactic surgery should not be performed in asymptomatic patients [41, 42].

31.3.4 Miscellaneous Conditions

Thymic carcinoid is rarely seen and mostly associated with multiple endocrine neoplasia type-1 (MEN-1) disease. Of all thymic carcinoids reported in the literature, 25% are related to MEN-1. Thus, a prophylactic thymectomy is suggested for patients undergoing subtotal or total parathyroidectomy [43].

Another condition that requires a thymectomy related to the parathyroid gland is parathyroid hyperplasia. In this disease, some of the recurrences after parathyroidectomy have been reported to occur from the parathyroid glands in the thymus gland. Therefore, a prophylactic thymectomy has been suggested, especially during parathyroidectomy in kidney-induced parathyroid hyperplasia [44].

Upper mediastinal lymph node metastasis is often observed in papillary thyroid carcinoma. Therefore, prophylactic upper mediastinal lymph node dissection with a sternotomy suggestion has been brought up for these patients. In a study investigating the necessity of prophylactic upper mediastinal lymph node dissection with a sternotomy, no difference in survival and disease-free survival was observed between groups with and without prophylactic dissection. Thus, this method was not recommended [45].

31.4 Conclusions

The development of anesthesia and surgical techniques paved the way for surgeries to be performed in less time and with less morbidity. Even major surgeries, which were described in recent case studies and could not be performed earlier due to high risk, can now be done using minimally invasive techniques. These developments can increase the examples of prophylactic interventions in thoracic surgery and enhance their application by thoracic surgeons.

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Prophylactic Surgery for Urologic Pathologies

32

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32.1 Introduction

Prophylactic surgery is also known as preventative surgery. It is novel for urologic surgery literature. Herein, we described "prophylactic surgery for urologic pathologies" according to published literature. Additionally, to our best knowledge, this is the first chapter for this issue in the literature. However, organ-preserving surgical modalities are very important urologic surgical procedures, and there is a separate place of prophylactic surgery.

We divided the genitourinary system anatomically and defined prophylactic surgery for urologic pathologies. We hope that this pioneer section would be a useful guide for clinicians.

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32.2 Upper Urinary Tract

32.2.1 Kidney Surgery

32.2.1.1 Preventive Nephrectomy

Both kidneys are valuable for homeostasis in the human body. However, one of them can be enough to survive without dialysis, and occasionally, bilateral nephrectomies should be performed for prophylaxis. This is sometimes indicated in association with end-stage renal disease (ESRD) managed with kidney transplantation [1]. However, ESRD is the part above the water, chronic kidney disease (CKD) is the part of an iceberg under the water. ESRD due to vesicoureteral reflux (VUR) is a prevalent notably in the paediatric population [2]. In this section, we described ESRD due to VUR. The importance of fixing VUR is described in another section below. However, it can be managed by medication, and when ESRD occurs, bilateral nephrectomies come into question. Of course, the suitable indications for the prophylaxis word are presented in the literature. This surgical procedure is performed as a prophylaxis for avoiding complications after kidney transplantation. The VUR process mostly begins from the prenatal period. Sargent revealed that 1/3 of patients who had a urinary tract infection (UTI) have VUR, and 9–20% of patients with prenatal hydronephrosis have VUR when tested in the postnatal period [3]. The VUR mentioned herein is primary VUR or secondary VUR, which is the cause of poste-

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rior urethral valve disease and/or lower urinary tract obstruction from the neurogenic origin, such as spina bifida. As a result, ESRD can be occurred due to VUR. Sometimes, VUR causes reflux nephropathy (RN), and indirectly, RN brings CKD, and a small number of patients progress to ESRD [4]. However, ESRD is rare in the paediatric population when it could not be managed with both medical and surgical treatments; as the most serious consequence, ESRD might be developed. Radiological examinations can easily show the degree of VUR (Fig. 32.1). Additionally, the VUR has been announced as one of the common causes of ESRD in children, in 2007, in USA [5].

The necessity of performing bilateral nephrectomy is for the prevention of complications after transplantation. Grade 5 VUR can cause voiding problems and UTI. Therefore, impaired urodynamic status can easily damage transplant kidney [6]. This can be performed before transplantation, meanwhile with transplantation. Papalois et al. (2000) reported that there was not any significant difference between preoperative or simultaneous patients who underwent bilateral native nephrectomy [7]. Fuller et al. found similar findings with them [8]. In addition, Ismail et al. noted that patients with simultaneous native nephrectomies and transplantation would need additional surgeries in short-term follow-up [9]. On the other hand, Glassman et al. (2000) reported higher patient satisfaction for concomitant native bilateral nephrectomy and renal transplant [10]. Kim et al. (2016) reported a higher risk of vascular diseases after concomitant surgery [11]. Elrggal et al. (2018) analysed all these in a review and found out that there are more advantages of concomitant surgery [12]. Over and above, when the laparoscopic nephrectomy is performed, the advantages could increase in the favour of the patients without and complications of graft kidneys [13].

One more point, when bilateral native nephrectomy is performed, bilateral ureters can be used for bladder augmentation [14]. Bellinger described the surgical technique [15]. Vascular source of the augmented ureters is always concerned. However, Kajbafzadeh et al. (2010) reported preserving vascularity of the ureter for augmentation [16].

Finally, simultaneous laparoscopic bilateral native nephrectomy and kidney transplantation seem safe in ESRD patients with grade 5 VUR [17]. Native ureters can also be used for bladder augmentation, especially in children. Bilateral native nephrectomy can be assumed as prophylactic urological surgery for upper urinary tract.

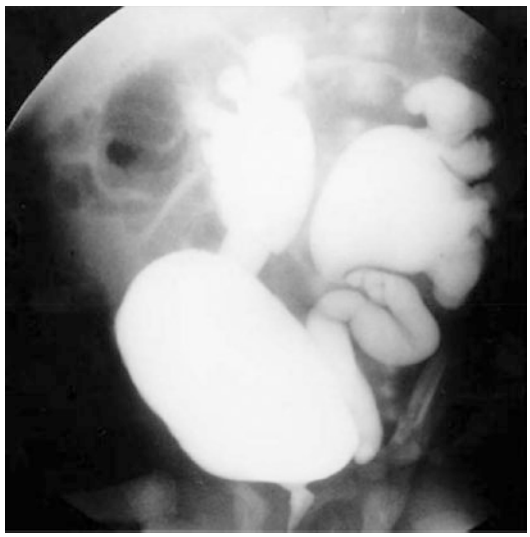

Fig. 32.1 A voiding cystourethrography of a patient with end-stage kidney disease. Grade 5 vesicoureteral reflux according to International Reflux grading system

32.2.1.2 Genetic Diseases

Autosomal dominant polycystic kidney disease (ADPKD) is a hereditary disorder, in which the ADPKD-1 or ADPKD-2 gene is mutated. Thus, synthesis of polycystin 1 or polycystin 2 proteins are changed [18]. Briefly, renal parenchyma is destructed by a renal cyst, which may become a huge size in the progress of the disease. ESRD occurs and half of the patients need dialysis or renal transplantation at the age of 60 years [19]. Sometimes, even the patient does not need renal replacement; it can take up a lot of space in the abdomen and make it difficult for the patient to breathe by pressing the diaphragm. Additionally, potential complications that may arise from pressure on other intra-abdominal organs are not the subject of this chapter.

Prophylactic nephrectomies come into question for patients with ADPKD notably, and they are listed in renal transplant. Sulikowski et al. (2009) evaluated ADPKD patients and making nephrectomies before, during and after renal transplant [20]. Moreover, Rozanski et al. (2005) agreed with them, as in the case of whom just ipsilateral nephrectomy is required; it should be performed before kidney transplant [21]. Laparoscopic nephrectomy is preferable; however, the size of the kidney might not be suitable for these surgical approaches. If the kidney size is over 15 cm, surgeons should consider this situation, as technical difficulties may occur [22].

Evaluation of all, we can easily suggest that bilateral, preferably laparoscopic, nephrectomy can be performed simultaneously with kidney transplantation in ADPKD patients.

32.2.2 Ureter Surgery

The VUR is defined as reflux of urine from the bladder to the ureter and/or renal pelvis [23]. VUR may lead to different clinical reflections, especially in children. VUR affects 1% of children, and it mostly causes UTI. If it is not been treated, it may lead to pyelonephritis, renal scarring and chronic renal insufficiency [24]. Recently, VUR is often questioned in children who have had a UTI. Contemporary surgical treatment is performed by endoscopic injection of non-animal dextranomer–hyaluronic acid [25]. Peters et al. described the endoscopic technique [26]. The success of treatment was defined as complete resolution of reflux when no VUR was demonstrated in voiding cystourethrography. Follow-up visits were stopped in the outpatient clinic for successfully treated children. Children who had persistent VUR were recommended reinjections [27]. Yu et al. (2006) reported the very successful rate of endoscopic treatment of VUR [28]. The endoscopic treatment can avoid complications of VUR, such as UTI. This is not meant to provide prophylactic endoscopic VUR treatment to every child with UTI. However, detailed clinical evaluation should be performed for this patient population. Indications of surgical intervention for VUR are listed by European Urology Guidelines on Paediatrics [29]. Our aim is just to consider urologists to diagnose and to treat VUR in its indications.

32.3 Lower Urinary Tract

32.3.1 Bladder Surgery

32.3.1.1 Bladder Diverticula

Bladder diverticula are typically classified as either congenital or acquired [30]. Acquired one can occur due to bladder outlet obstruction or neurogenic bladder. Most of the bladder diverticula are asymptomatic and are commonly discovered during the investigation for haematuria, lower urinary tract symptoms or infection. However, some can also be found incidentally during radiographic examinations [31].

Bladder diverticula can be managed in different ways, including conservative non-operative management, surgical excision and endoscopic management. Indications for treating bladder diverticula include urinary infection, stones or malignancy. Of course, malignancy needs to be managed according to tumour types and levels. Endoscopic management includes fulguration [32]. Surgical management includes, basically, excision of the diverticula [33]. In the case of some clinical findings that are listed above, surgical/endoscopic treatment of bladder diverticula can provide clinical improvement in patients. Additionally, bladder diverticula do not have a muscular wall beyond the mucosal layer. This potentially can be resulted in increased risk for extension of possible malignancy outside the bladder. Thus, prophylactic diverticulectomy can avoid this. However, laparoscopic and/robotic-assisted laparoscopic operative techniques have been announced as safe and effective for surgical treatment of bladder diverticula [34]. Endoscopic or surgical intervention should be preferred according to diverticula and the patient's clinical situation [35].

32.3.1.2 Bladder Augmentation

Neuropathic bladder (NB) is a heterogeneous clinical entity that can result from a variety of conditions affecting the central or peripheral nervous systems. Myelodysplasia, specifically spina bifida, remains the most common cause of NB in the paediatric population [36]. The management of NB aims to preserve the native bladder to store urine at low pressure and to allow efficient emptying of the bladder. Additionally, to keep quality of life is another target of clinicians during the management of NB. Early management is usually focused on preventing irreversible injury to either the upper or lower urinary tract. Evaluation of NB is not the topic of this chapter. Over 29 years, clinicians have been routinely using clean intermittent catheterization (CIC) at the first step of NB management [37].

Medical management includes using anticholinergic/beta3 mimetic [38], and endoscopic interventions might be used in the case of not responding to medical treatment [39]. Botulinum A is used in endoscopic management of NB [40]. Surgical treatment as augmentation cystoplasty seems optimal when medical and endoscopic interventions are not sufficient for NB [41]. The surgical technique is used as Szymanski et al. (2015) described [42]. This surgical modality leads to keep a high quality of life as possible [43]. Additionally, to protect the upper urinary tract is very important to make augmentation cystoplasty for delayed or absent kidney failure as much as possible. However, bladder augmentation is the reference standard surgical procedure used to increase bladder capacity and reduce storage pressures; it has some serious risks for long-term. [44]. Bladder calculi, possible metabolic derangements, vitamin B12 deficiency and in long-term, some malignancies might occur [45]. On the other hand, in patients who have physical or cognitive barriers to compliance with CIC, vesicostomy has come into question as a surgical treatment of NB [46]. Furthermore, some incontinent diversions might also be performed [47]. Despite there are some complications in long term, significant advantages of bladder augmentation cystoplasty are performed to preserve bladder and upper urinary tract. Therefore, if there is no contraindication, such as inflammatory and congenital bowel disease, augmentation cystoplasty should be done before the patient develops kidney failure. When ESRD occurs, the management of the disease will be complicated. Besides, performing simultaneously kidney transplant and bladder augmentation is still a subject of debate. However, Capizzi et al. (2004) have reported kidney transplantation in children with reconstructed bladder [48]. This is a well-known truth that wound and tissue healing would be delayed in patients with renal failure [49]. Thus, performing both procedures simultaneously are reasonable. Additionally, decreased risk of infection of the allograft, two anaesthetics, difficult dissection and the possibility of damaging the arterial supply of the augment may be avoided.

32.4 Prostate Surgery

32.4.1 Chronic Prostatitis

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a condition of chronic pelvic pain among the men and accounts for 80–95% of all symptomatic prostatitis cases [50]. The aetiology and pathogenesis are still not clear. Thus, the optimal treatment of CP/CPPS is a subject of debate. Infections, chemical irritation, trauma, genetics, and psychological stress that result in some subsequent neurological changes, such as brain microstructural changes, central sensitization, and pelvic floor spasms, have been claimed for trigger factors [51]. A combination of alterations to the nervous system with endocrine, psychosocial, or immunological abnormalities leads to the chronic state of CP/CPPS [52]. Chronic bacterial prostatitis and chronic pelvic pain syndrome are common diagnoses in urology and represent a relevant health problem [53].

Sometimes, medical and minimally invasive treatment options cannot be enough to heal the symptoms [54]. The main goal of this chapter is to discuss surgical treatment options for chronic prostatitis, notably to face prophylactic modalities.

Transurethral resection of the prostate (TURP) is advocated for CP/CPPS based on a few anecdotal experiences, but there are absolutely no reliable data or experiences to substantiate a treatment effect [55]. Patient with significant lower urinary tract symptoms with a background of CP/CPPS may benefit from this therapy [56]. Especially, the optimal therapy for category 2 and 3 prostatitis is still not clear, and surgical options might prove to be a viable alternative. In the systemic review by Schoeb et al. (2017), 110 TURP cases and 21 radical prostatectomies for CP/CPSS were evaluated [54]. At this point, we have to emphasize that performing radical prostatectomy for these patients is controversial. Additionally, ethical aspects have come into mind. All these patients had CP/CPPS type 2 and 3 patients. TURP for CP/CPPS patients should be evaluated in clinical council and radical prostatectomy, and of course, it should not be the first surgical choice. If the surgery is preferred, complete removal of inflamed or infected prostate tissue should be performed. Therefore, holmium laser enucleation seems a plausible option that can easily remove all prostate tissue [57]. To perform surgical treatment for CP/CPSS, as TURP at the first step, is not mentioned in the guidelines. This is because most of the CP/CPSS patients are young, male and complications of the TURP, such as retrograde ejaculation [58, 59]. More clinical trials are needed to find out optimal surgical interventions for CP/CPSS. However, prophylactic surgical treatment for CP/CPSS can be defined in the future.

32.4.2 High-Bladder Neck Elevation

Bladder neck elevation (BNE), which indirectly reflects prostatic urethral angle (PUA), can be a cause of bladder outlet obstruction (BOO) and BOO-related symptoms [60]. We know the starting age of BOO due to benign prostatic hyperplasia (BPH); however, BNE can cause to BOO in younger ages. Medical management options are similar to BPH [61, 62]. In the lack of response to medical management, surgical options come into question. Because of the side effects of TURP, clinicians would not perform at the first step in the management of BNE [63]. However, ejaculation preserving endoscopic surgical techniques were described during TURP [64]. Nonetheless, patient selection is very important for this indication. Thus, preoperative cystoscopy can be performed to define BNE and to measure bladder neck angle. If the angle is >35°, surgical treatment options might be more beneficial [65]. To perform endoscopic prostate incision and/or TURP is dependent according to prostate size and grade of obstruction [66]. In the name of prophylactic surgery, TURP/prostate incision should be considered in patients with BNE. However, as it is mentioned above, it depends on patient complaints, prostate volume and bladder neck angle.

32.5 Penile Surgery

However, male circumcision is usually practised for routine and religious reasons; this is one of the most suitable surgeries for the definition of prophylactic surgery. Besides, circumcision is mostly performed on the penis without any pathology.

32.5.1 Circumcision

Circumcision has a long history, dating back to 4000 BC [67]. Besides Jewish communities have traditionally practised circumcision on the eighth day of life since 1800 BC, the age of circumcision widely change in the Muslim community [68]. Additionally, circumcision is performed in some of the African communities and certain Australian indigenous tribes since ancient times [69, 70]. Circumcision is also one of the most frequently performed surgery worldwide [71]. Morris et al. (2016) revealed that nearly 33–37% of the males are estimated to be circumcised [72]. There are many surgical techniques for circumcision [73].

For the purposes of this book and chapter, circumcision can prevent the development of UTI and penile cancer and help to reduce the human immunodeficiency virus (HIV) transmission. Shapiro et al. (1999) concluded that UTI is more

frequent in uncircumcised men. This might be related to bacterial colonization in foreskin [74]. Moreover, circumcision may play an essential role to prevent VUR in boys. UTI and renal scar due to VUR can be avoided by circumcision [75]. Mukherjee et al. (2009) commented that the positive effect of circumcision is to prevent UTI in boys with posterior urethral valve [76]. Furthermore, Morris et al. (2013) published lowered risk of UTI in a lifetime in circumcised man [77]. Nonetheless, UTIs can be managed conservatively with antibiotics without renal tissue loss [78]. More studies are needed to prove this issue.

There is no doubt that circumcision was historically quoted as a preventative measure for the future development of penile carcinoma. Invasive penile cancer is strongly associated with phimosis, that is, of course, the risk can easily be removed by circumcision [79]. In a study that makes this situation contradictory, Sewell et al. (2015) reported the incidence of penile cancer in the USA is similar to that in Australia even though circumcision rates in the USA are significantly higher [80]. Except for prepuce and related diseases, there are some factors that can predispose penile cancer, such as genital hygiene, tobacco usage and other sexual transmitting diseases [81]. It is obviously clear that circumcision may not stop penile cancer but can reduce the risk.

Studies from Africa proved that male circumcision can protect against acquiring HIV among heterosexual men [82]. The exact mechanism is based on removing parts of the foreskin that are most susceptible to infection by the virus [83]. These do not mean that circumcision is definitely avoiding HIV transmission. Thus, safe sex comes into question [84]. Nevertheless, circumcision is not enough to stop HIV transmission, but it can reduce. More strategies are needed to stop HIV transmission both for men and women before and during sexual intercourse.

Balci et al. (2015) revealed the risk of 9% oncogenic human papillomavirus (HPV) in the foreskin in pre-pubertal boys [85]. This is another benefit of circumcision that possible reducing HPV in the pre-pubertal boys and their future partners.

In the light of all above, it is seen that circumcision might be also accepted as one of the prophylactic procedures that can prevent UTI in boys, reduce penile cancer and HIV transmission in heterosexual men.

32.5.2 Urethral Surgery

32.5.2.1 Urethral Valves

Posterior urethral valve (PUV) occurs in 1:4000 to 1:25,000 of live births, and clinical presentation of PUV considerably varies [86]. PUVs are the most common causes of bladder outlet obstruction in children. Despite medical management, PUV may lead to serious inabilities, such as renal insufficiency and incontinence [87]. Rapid diagnosis and treatment are essential. Endoscopic resection, which has been accepted as a definitive surgical treatment, is still maintaining its importance in the treatment of PUV [87].

Follow-up methods may still be a subject of debate after PUV resection. However, a strict follow-up schedule would be better for preserving bladder and kidney functions. Additionally, the serum creatinine may be an indicator of better outcomes in long-term follow-up. Routine cystoscopy and voiding cystourethrography are the preferred ones. Furthermore, routine uroflowmetry can be another tool during follow-up.

Nevertheless, PUV should be operated as soon as it is diagnosed. Thus, bladder and kidney dysfunctions (notably ESRD) caused by PUV can be prevented.

32.6 Testicular Surgery

Undescended testis (UDT) is common in paediatric ages. Because of UDT being the most common genital disorder identified at birth, the diagnosis can be performed very easily and rapidly [88]. The position of UDT might vary and be located in the abdominal cavity, inguinal canal or subcutaneous cavity, which could determine the extent of the associated phenotype. The main reasons for treatment of this remain reducing the

risks of impairment of fertility potential, testicular malignancy, torsion and/or associated inguinal hernia. Therefore, orchiopexy is the most successful therapy to relocate the testis into the scrotum without any additional hormonal therapy (that is also not recommended) [88]. Therefore, it should be operated in childhood to prevent all pathologies, previously addressed as orchiopexy, and is recommended for testes that remain undescended after 6 months of age [89].

32.6.1 Orchiectomy for Undescended Testis in the Adult

The risk of developing testicular cancer due to UDT is increased to 5–10 times that of the general male population. This increased risk for a UDT or previously cryptorchid individual is indicative of long-term damage, despite early orchiopexy in many cases [90]. The association between UDT and testicular germ cell tumour has been well documented since the 1940s. UDT is an accepted risk factor with a relative risk of 3.7–7.5 times higher than the scrotal testis population [91]. If UDT is bilateral naturally, the risk of testicular cancer is higher than unilateral one. Moreover, Peterson et al. published that if the UDT is corrected after 13 years old, there is two times more the risk of cancer occurring than in patients underwent surgery before 13 years old [92]. Nevertheless, there is increased risk of testicular cancer in UDT patients [93].

However, diagnosis of UDT is often delayed for reasons, including patient unawareness or denial of abnormal findings in the testis [94]. Moreover, the UDT loses its function by the time [95].

Patients with a single testis or bilateral postpubertal UDT, preservative treatment might be considered, although such treatment requires careful follow-up [96]. Additionally, careful observation may be considered in patients over 50 years of age with palpable UDT. Lifelong, regular self-examinations are needed for patients with UDT, even though they had been operated. In view of all these, orchiectomy should be performed for UDT after puberty with some exceptions. Another point of view, prophylactic orchiectomy is needed with patients with UDT after puberty.

Last but not least, taking a biopsy from the contralateral testis might be needed to rule out germ cell neoplasia in situ and either take the pertinent prophylactic treatment, as it is a pre-cancer lesion, or to inform the patient about the risk. Clinicians should take into account that orchiectomy might be indicated in some cases when the patient is not suitable for local radiotherapy or prefers orchiectomy for whatever reason [97]. Additionally, for some congenital syndromes (e.g. Klinefelter) that are associated with multiple testicular microlithiasis, a testicular biopsy may be indicated.

32.7 Adrenal Surgery

It is obviously clear that day by day, urologists are beginning to have a say in adrenal surgery. The most recent approach in adrenal surgery is partial adrenalectomy with robotic surgery [98]. On the other hand, when there is insufficiency and/or failure in the treatment of pituitary Cushing and unlocalized ectopic Cushing's syndrome (CS), bilateral adrenalectomy may be considered [99]. Pituitary-dependent Cushing's disease (CD) is the cause of endogenous CS, and transsphenoidal resection of a pituitary tumour is the first line of treatment option for the patients of CD. Unfortunately, the operation fails 30% of the CD cases.

Moreover, in patients of CS with bilateral adrenal pathology, bilateral adrenalectomy is the obvious treatment option. Nevertheless, all these clinical entities could be indications for bilateral adrenalectomy for preventing severe clinical symptoms of CS. However, it's overall morbidity and mortality is higher than other endocrine operations [99]. The operation should be discussed with the patient, considering clinical symptoms and pros and cons. Minimally, invasive approaches should be preferred. If there is a robot option, it should be considered first for adrenal surgery.

32.8 Conclusions

At first glance, something does not come to mind for urological prophylactic surgery; we evaluated the published literature from point of view of the urologists. Therefore, bilateral nephrectomy, endoscopic VUR correction, diverticulectomy, bladder augmentation, endoscopic prostatectomy and prostate incision, PUV resection, circumcision, orchiectomy and bilateral adrenalectomy are evaluated for prophylactic urologic surgeries in individual indications. Some of the emerging genetic findings on the relationship between BRCA genes and prostate cancer have not been proven definitely. Thus, we would not want to discuss these. Prophylactic urological surgeries may vary with increasing procedures and indications in the future. We hope this section of the book can help to keep prophylactic surgery in mind in its indication for clinical practice of urologists.

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33 Prophylactic Procedures in Pediatric Surgery

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33.1 Introduction

Prophylactic surgery, which is done to prevent diseases that may develop later in a healthy tissue or organ system, maybe more important in children than in adults because of the long-life expectancy in children. Although the topics are generally similar to those encountered in adults, while deciding on prophylactic surgery in children, the age factor, the psychological state of the patient and his family, the presence of concomitant congenital diseases, and the long-life expectancy change the decision-making processes. Here, we tried to summarize the reasons and age groups of prophylactic surgical interventions, which are applied frequently in children today, in the light of current literature information.

33.2 Prophylactic Surgery for Contralateral Inguinal Hernia

Inguinal hernia repair is one of the most common surgical interventions performed among children and presents in approximately 0.8–4.4% of the children [1, 2]. Management of a contralateral groin is still controversial since it has been discovered that all contralateral patent processus vaginalis (PPV) do not develop an inguinal hernia. A PPV is not a clinical condition, where it becomes a problem when it is large enough to allow pass intra-abdominal contents into the sac. Processus vaginalis (PV) closes in the first 2 months after birth in 40% of the infants and 60% of the children at age 2 years [3]. The remaining PPV rate of 40% did not decline significantly in teenagers [4]. The reported incidence of metachronous contralateral hernia (MCH) is varying in several reviews between 7 and 10%, which indicates the necessity of carefully patient selecting for intervention to the contralateral side [5–7].

The detection of an MCH was done with herniography and pneumoperitoneum in previous years, but these technics have been abandoned because of its drawbacks and unreliability [8]. The examination of the contralateral side may be done using laparoscopy via a transumbilical port or a 70-degree laparoscope by passing through the operated hernia sac with a sensitivity and specificity over 99% [2]. Also, in a meta-analysis of Dreuning et al. (2019), they have reported that preoperative ultrasonography has a high sensitivity (88%) and specificity (93%) for detecting PPV [9].

The advantages of the repair of the asymptomatic side include avoiding second anesthesia, reduce patients' and parents' anxiety, reduce the risk of incarceration, and reduced costs. Besides this, an unnecessary intervention has the risk of

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injury to the spermatic cord, wound infection, hematoma, testicular atrophy, increased pain, prolonged operation and anesthesia risk, and increased costs [1].

Since time, there is a decline in the routine contralateral exploration regarding the large reviews and meta-analyses. Historically, many surgeons performed bilateral exploration in the presence of unilateral hernia according to the age or gender of the patient or the side of the hernia. It has been thought that in premature patients, girls, and left-side hernias, the contralateral exploration must be carried out because of the high risk of an MCH. These approaches have been abandoned because multiple studies revealed that the wait-and-see method is reliable with only a 0.5–2% complication rate, and 10 patients must be operated to cure one MCH [10–13].

Nowadays, contralateral exploration is recommended for children at risk of having MCH more than healthy patients. In patients who have ventriculoperitoneal shunts or peritoneal dialysis catheters, there is excess fluid and pressure in the peritoneal cavity, and the hernias are mostly bilateral. In these patients, the contralateral side must be explored in the case of clinical unilateral hernia since it has been documented that incarceration is a great risk, and spontaneously, obliteration of a PPV is not likely [14, 15]. Patients with connective tissue diseases like Hunter-Hurler, Ehlers-Danlos, Marfan's or cutis laxa syndrome, chronic pulmonary disease, or high-risk patients with cardiovascular or neurologic problems, in whom second anesthesia has to be avoided, are candidates to the contralateral exploration for an MCH [12, 16].

In conclusion, a contralateral exploration is not mandatory in all patients with an inguinal hernia. The risk and advantages of this intervention for each child must be evaluated on a personal basis.

33.3 Prophylactic Resection for Meckel's Diverticulum

Meckel's diverticulum (MD) is the most commonly encountered anomaly of the gastrointestinal tract (GI) and is caused by incomplete obliteration of the omphalomesenteric duct during gestation. The reported prevalence is between 0.3 and 2.9% of the general population, but the majority of the patients are asymptomatic for life, where symptomatic cases are almost in the earliest years of life [17–19]. MD is symptomatic due to intestinal obstruction, GI bleeding, and diverticulitis with or without perforation. There is no controversy about to resect every symptomatic MD in all patients of any age, but an incidentally discovered asymptomatic MD is still a surgical dilemma.

Only 4% of the patients with an MD are symptomatic, and more than 50% of patients of the symptomatic patients are under the age of 10 [20, 21]. In this group, the majority is under age <1 year, wherein the adolescents and adult patients, the majority is in 11–30 years of age [22]. There is also a male predominance among symptomatic patients with a 2.9:1 male to female gender ratio. The length and width of MD are reported with a mean length of 3.05 cm and a diameter of 1.58 cm in a review of Hansen et al. [23]. In several reports, it has been mentioned that MD in symptomatic patients tends to be longer with a narrower base [22, 24]. The presence or absence of ectopic tissue is the most significant determinant for the need for surgical removal of MD. Palpation of the thickening of MD is investigated and demonstrated no association, but a wider diverticulum base was reported in the study of Slívová et al. (2018) [25, 26].

Under this knowledge, the question is that, does it worth resecting an asymptomatic MD and faces the possible complications of a bowel resection? Zani et al. (2008) declared in their review article that postoperative complication rates after prophylactic resection reach 5.3%, where 1.3% of children with an MD left in situ have symptoms with time [20]. In an epidemiologic, population-based study of Cullen et al. (1994), they stated that the risk did not decrease with age, so they recommended resection of all encountered MDs, except in the presence of additional conditions like generalized peritonitis [27]. Also, some authors support resection because of the life-threatening clinical course in some patients with MD, where others are against it after encountering life-threatening complications

after prophylactic resections [28, 29]. In children, it has been found that MD-related complications are higher in children younger than 8 years of age than older children [30].

In conclusion, it has been recommended that leaving an incidental MD in situ is mandatory, which is identified on imaging studies. Asymptomatic MD found during abdominal exploration in early ages of life, one should resect the MD. In young adults <50 years of age, especially men, MD's longer than 2 cm, and with an associated anomaly on palpation, resection must be carried out. In elderly patients, no resection is recommended in the appearance of a normal-appearing MD.

33.4 Prophylactic Surgery for Intestinal Malrotations

Intestinal malrotation is a rare congenital anomaly of intestinal position with an incidence of 3.9 per 10,000 live births according to the report of the Centers for Disease Control, where other reports an incidence of 0.2–1% in the pediatric population [31, 32]. Malrotation is a result of an error in intestinal rotation and fixation of the intestinal mesentery. The duodenojejunal junction lies at the right side of the midline close to the ileocecal valve causing a relatively narrow mesenteric stalk. This anatomical deficit may cause midgut volvulus, followed by ischemic bowel, possible short gut syndrome, and death.

Most of the patients are symptomatic under the age of 1, where 50% of patients are in the newborn period [33]. The sudden onset of the symptoms after volvulus is typical at this age with bilious vomiting, abdominal distension, abdominal tenderness, peritonitis indicating perforation, and rectal bleeding indicating bowel ischemia at later phase. In later childhood, the symptoms become more atypical like cyclic vomiting (often non-bilious), recurrent abdominal pain, and failure to thrive [34].

The surgical procedure for malrotation was described by Ladd in 1936 as detorsion of the volvulus, division of the Ladd's bands, widening of the mesenteric root, and positioning the small bowels to the right and the large bowels to the left quadrants of the abdomen [35]. Some authors added prophylactic appendectomy to this original procedure to avoid misdiagnosis of a left lower quadrant appendicitis, where others have discouraged this maneuver to avoid associated complications [36]. Although the laparoscopic repair of volvulus in a neonate was described by van der Zee et al. in 1995, this approach is still not performed routinely in infants and children as the first choice [37, 38].

The treatment of malrotation in symptomatic children has been well established, but the treatment of malrotation in an asymptomatic child or malrotation diagnosed incidentally remains controversial regarding the need and the timing of the operation. Some clinical conditions may be associated with malrotation or nonrotation like congenital diaphragmatic hernia (CDH), omphalocele, gastroschisis, congenital heart disease (CHD), and heterotaxy syndrome (HS), for which prophylactic Ladd's procedure remains a matter of debate [39].

Surgical correction of malrotation with or without symptoms is warranted for infants because of the high risk of volvulus at this period [40]. It is also not clear how much the risk of volvulus decreases within years of age because there are also reported patients' malrotation with volvulus in age 70s [34]. In the report of Prasil et al. (2000), they have the charts of patients operated on for malrotation in means of age (<2 or >2 years old). They have found that 17.2% of patients older than 2 years have volvulus and recommended surgical attention in all patients regardless of age [41]. Malek et al. (2006) designed a model of the probability of a Ladd's procedure and reported that most patients with malrotation will undergo this operation in childhood. They recommended careful observation of adults with asymptomatic malrotation for unusual or unexplained abdominal discomforts associated with a partial or total volvulus [42]. In a recent review of American Pediatric Surgical Association on asymptomatic malrotation, they have stated that upper gastrointestinal studies remain the best imaging modality for malrotation, but even ultrasound cannot be used to rule our malrotation or volvulus, and the narrow-based mesentery cannot be determined with

imaging studies as a predictor of volvulus in the future. As a Grade C recommendation, they said to operate on asymptomatic patients who are "younger at age" without given a specific age [43].

In conclusion, it is a fact that labeling of any malrotation as "asymptomatic" is not reasonable because many patients have been thought of as asymptomatic-declared abdominal symptoms at carefully taken history. To prevent the catastrophic results of midgut volvulus, prophylactic surgery for malrotation is recommended in all patients at low risk for postoperative morbidity or mortality.

33.5 Prophylactic Fecal Diversion

Fecal diversion in children is used for several aims; it is mainly used to divert the fecal stream for decompression, for emergency salvage, and before the reconstructive correction of the lower colorectal anomalies.

After the initial management of the patient with a traumatic wound, it is crucial to achieve a proper infection control for the prevention of sepsis and establish a good wound healing. In patients with severe full-thickness perineal and gluteal burns, open pelvic traumas, or colorectal traumas, fecal contamination may be prevented with a temporary-diverting colostomy [44–46]. It is also beneficial for giving the child a favorable long-term functional outcome by reducing the depth of the wound, facilitating wound care, and reducing the debridement frequency in the operation room.

A protective colostomy in anorectal malformation (ARM) is needed to avoid contamination before the definitive operation [47, 48]. An infection and dehiscence is the most unwanted situation after ARM repair because there is a greater risk of damaging the continence mechanism, and secondary procedure is much complex than the primary one [49]. In patients with flat perineum, meconium-stained urine, bowel gas above the coccyx, and cloaca receive a diverting colostomy, preferably located at the descending colon [50]. The distal part of the stoma may be created as a mucous fistula to avoid prolapse [47]. After the definitive repair, the colostomy is closed after reaching the appropriate size of the anus.

Another group of patients, who need a fecal diversion, are the patients with inflammatory bowel disease and familial adenomatous polyposis coli [51]. After initial subtotal or total colectomy in patients with ulcerative colitis and familial polyposis, it has been reported that a temporary loop ileostomy prevents anastomotic leak from the created ileal pouch and reduces overall complication rate [52]. In Crohn's disease (CD) patients, the role of diversion is to allow healing of perianal disease and induce remission in refractory colonic and perianal CD [53, 54]. Although this approach has a high incidence of disease remission, intestinal-continuity restoration rates differ between 10 and 39% in various reports [53, 55].

33.6 Prophylactic Incidental Appendectomy

In a patient without acute appendicitis findings but undergoing laparotomy for other reasons, the appendectomy is called prophylactic incidental appendectomy (IA) [56]. However, planned appendectomy in absence of appendicitis or another surgical procedure is called elective appendectomy [57]. However, this surgical procedure is a controversial issue because of potential complications. An easy surgical procedure, no additional anesthesia, lower morbidity rate, and exclusion of difficulties in diagnosing appendicitis in the future are the benefits of the IA [58]. Prolonged operation time, increased morbidity, and transformation of the process from clean to clean-contaminated due to colonic flora are undesirable features of IA [58]. Besides, the appendix is increasingly being used in urological and biliary reconstructive surgeries and for colonic irrigation in bowel management [56]. Due to all these advantages and disadvantages, the decision of whether to make IA or not has been considered more (Table 33.1) [56].

Considering the developments in the use of appendix for reconstruction in recent years, the

Table 33.1 Summary of recommendations

Condition	Recommended	Not recommended
Malrotation	Yes, to prevent future misdiagnosis [59]	It may require for bowel/bladder incontinence and a long-term gastrostomy [60, 61]
Congenital diaphragmatic hernia	Yes, to prevent later atypical appendicitis [62]	When a patch is required for repair, due to increased risk of contamination [63]
Oncologic surgery	Yes, neutropenia may hide the symptoms of peritonitis [64]	Appendectomy during Wilms' tumor surgery does not change the postoperative complication rate [65]
Anorectal malformations and exstrophy	Not [56]	Due to high rate of intestinal/bladder incontinence [56]
Neurological diseases, ventriculoperitoneal shunt, hydrocephalus, etc.	Not [56]	Due to high rate of intestinal/bladder incontinence [56]
Cystic fibrosis	Maybe yes in the cystic fibrosis, in order to irrigate meconium [66]	Unclear in other circumstances [56]
Hirschsprung's disease and chronic constipation	Not [56]	For *antegrade* continence enema in bowel management [56]
Incidentally discovered fecalith	Yes, it may be, depending on the patient's easy access to healthcare[56]	
Biliary atresia and choledochal cysts	Not [67]	Due to the possibility of its use in biliary reconstruction [67]

comorbid conditions of the patient should be considered before performing IA. Advances in minimally invasive surgery make the decision even more difficult. The long-life expectancy in children, the additional medical history, and the possibility of using appendix as a tubular channel should be rigorously evaluated during the decision-making process [56].

33.7 Prophylactic Cholecystectomy

Prophylactic cholecystectomy (PC) is defined as the removal of the non-diseased gallbladder when laparotomy is being undertaken for other reasons.

Choledochal cysts cause many complications, such as ductal stricture, stone formation, cholangitis, rupture, and secondary biliary cirrhosis. In addition, the risk of choriocarcinoma, pancreas, and gallbladder cancer risk increase 20–30 times compared to the normal population [68]. While the incidence of malignancy in cysts is 0.4% under the age of 18, it reaches 11% in all adults and 38% over the age of 60. The presence of abnormal pancreaticobiliary junction (APBJ) in cysts increases the risk of malignancy [69]. APBJ alone increases the risk of pancreatic and biliary malignancy, even without cyst or ductal dilatation. Especially gallbladder cancers are common in APBJ patients without cysts. Prophylactic cholecystectomy is recommended in these patients [70].

The incidence of gallstones has increased in patients with short bowel syndrome (SBS). In one study, gallstones were detected in 4 of 24 patients who underwent ileal resection in the neonatal period [71]. This rate rises up to 44% in adult ages [72]. Cholelithiasis causes more complications in patients with SBS compared to the general population. Approximately, half of the patients with SBS go to recurrent laparotomies. Prophylactic cholecystectomy is a reasonable procedure to be performed safely and without causing any complications [73]. In general, urgent intervention requirements may be required because patients with SBS undergo multiple operations. In such cases, cholecystectomy may not be recommended. Also, the issue of whether prophylactic cholecystectomy causes intestinal

dysfunctions and hepatic diseases in patients with SBS has not yet been clarified [73].

Splenectomy is recommended for the treatment of hereditary spherocytosis (HS) in children. During the same operation, cholecystectomy should be performed if there are stones in the gallbladder. If there is no stone, prophylactic cholecystectomy is not recommended. In a study, stone formation was not observed in the follow-up of patients without cholelithiasis during splenectomy [74].

33.8 Prophylactic Splenectomy

Prophylactic splenectomy can be defined as the removal of the spleen, which is actually disease-free, which exaggerates one or more of its normal functions in order to contribute to the treatment of some special hematological diseases in children. Splenectomy is indicated in patients with (HS), auto hemolytic anemia, and thalassemia because in any case, the spleen causes excessive hemolysis [75].

HS is the most common cause of hemolytic anemia, although it is rarely seen. It occurs due to a defect in the red blood cell membrane. Prophylactic splenectomy is effective in improving anemia in patients with severe hemolysis. Partial splenectomy may be preferred in children under the age of 6. Compared with total splenectomy, partial splenectomy also has a lower risk of sepsis of encapsulated bacteria. If necessary, a total splenectomy can be delayed until after the age of 6 [76].

Acute splenic sequestration crisis observed in sickle cell disease is a serious complication that requires prophylactic splenectomy. In the past, splenectomy was not recommended before 5 years of age because of fear of postsplenectomy sepsis. Recently, reports are indicating that splenectomy can be done at an earlier age with appropriate vaccination and prophylactic antibiotics [77].

Also, prophylactic splenectomy is performed since the spleen is responsible for platelet destruction as in idiopathic thrombocytopenic purpura. Splenectomy is usually a suitable option for a small percentage of chronic ITP patients with severe thrombocytopenia and hemorrhagic symptoms and requiring repeated pharmacological interventions. Although splenectomy is effective in most patients, rates of splenectomy among children with ITP have decreased significantly since the early 2000s, especially among children under 5 years of age [78]. While the cause of the decline is not clear, it may be associated with an increased availability of effective second-line treatments.

33.9 Prophylactic Surgery in Pediatric Surgical Oncology

Prophylactic surgery in children with certain cancer predisposition syndrome may decrease the incidence of malignancy. It is superior due to low complication rate and high cost-effectiveness compared to conventional screening and routine examinations [79].

33.9.1 Familial Adenomatous Polyposis

Colorectal cancer is seen in 1/471 rate in familial adenomatous polyposis (FAP) patients before 20 years of age [80]. The risk of developing cancer during life is approximately 100%. In general, three prophylactic surgical methods are used: total proctocolectomy with ileal pouch-anal anastomosis (IPAA), total abdominal colectomy with ileorectal anastomosis (IRA), and proctocolectomy with ileostomy [81]. The timing and age of prophylactic colectomy are uncertain because the data are limited in terms of surgical results in children. In classical FAP, the timing of surgery is done between the ages of 15 and 25, depending on age, compliance, presence of dysplasia/cancer, genotype, and the number of adenomas [81]. The most appropriate age should be determined according to the psychological compliance of the young patient to aggressive surgery. IRA or IPAA options are determined according to the number and/or size of polyps,

postoperative follow-up compliance, and family's common sense. Patients undergoing IRA develop 30% rectal cancer until age 60. IPAA is more advantageous in terms of optimal bowel control. As can be seen, discussions on the timing, size (extend) of surgery, and the types of reconstruction continue in pediatric FAP management [79].

33.9.2 Medullary Thyroid Cancer

In children, the thyroid gland is particularly sensitive to irradiation and carcinogenesis. Unlike adults, thyroid cancers show regional lymph node and distant organ metastasis at the time of diagnosis. Despite these characteristic features, thyroid cancers in childhood have a good prognosis. Medullary thyroid carcinoma (MTC) in children is detected either as a solitary nodule or due to the presence of MTC in one of the family members and typically as part of MEN2A or MEN2B.

Total thyroidectomy performed with central neck dissection in children with RET gene mutation is the standard prophylactic surgical approach. Early total thyroidectomy seems to be effective in preventing the development of MTC in the long term [82]. However, due to insufficient data, performing prophylactic surgery, especially based on RET gene positivity, especially in the early (under 2 years) period may cause unnecessary thyroidectomies [83]. Compared to adults, thyroidectomy complications are much higher in children, and especially infants. In very young children, it is very difficult to distinguish parathyroid glands from surrounding tissues during surgery. Although the complication rate of experienced surgeons is quite low, postponing thyroidectomies under the age of 2 should be considered [79]. However, the American thyroid association (ATA) has revised the MTC guidelines on disease management [84]. Today, the decision on the timing of prophylactic thyroidectomy is not based solely on DNA analysis. In addition, clinical data and most importantly, basal or stimulated serum calcitonin level is used. The ATA revised guidelines identified the highest-risk, high-risk, and moderate-risk groups for prophylactic thyroidectomy in children. In those at the highest-risk group, thyroidectomy should be performed in the first year of life, even in the first months of life. Prophylactic thyroidectomy should be performed at the age of 5 or earlier considering the serum calcitonin levels in the high-risk group. Timing in the medium-risk group should be based on high serum calcitonin levels. It can be extended for several years or even 10 years with 6-month or 1-year evaluations [79].

33.10 Conclusion

As can be understood from the abovementioned diseases, when performing a prophylactic surgical procedure, the benefit-harm balance, the risks that may develop later in life, the psychological conditions of the patients and their parents, and the age group to be applied should be carefully evaluated.

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34 Prophylactic Surgery for Neurosurgical Pathologies

Nurullah Yüceer

34.1 Introduction

Neurosurgical pathologies, in which the most prophylactic surgery is performed, are brain tumors, cerebrovascular diseases, craniospinal injuries, congenital and degenerative diseases. As a neuroradiological examination in patients suspected of intracranial pressure increase as a result of clinical evaluations, the most commonly used diagnostic methods today are magnetic resonance imaging, computed tomography (CT) and angiography with direct radiographs. Timing of prophylactic surgery differs among these pathologies. It is preferred that the timing of prophylactic surgery is limited to days in cerebral aneurysms. The timing of prophylactic surgery in brain and spinal tumors can be limited to weeks. The prophylactic surgery timing in congenital and degenerative patients can be within months. Neurological examination is normal in the majority of patients scheduled for prophylactic surgery. The results are very good in these patients who underwent prophylactic surgery [1, 2].

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34.2 Increased Intracranial Pressure and Hydrocephaly

Increased intracranial pressure reflects changes in the brain, cerebrospinal fluid (CSF) and blood volume that make up the intracranial structures. Intracranial pressure is 10–15 mmHg in adults and older children, 3–7 mmHg in young children, 1.5–6 mmHg in newborns. In patients with increased intracranial pressure, headache, nausea and vomiting and bilateral papillary edema are typical. Hydrocephalus is an abnormal, usually progressive accumulation of CSF within the ventricular system that distends the ventricles and often raises. The main causes that can lead to hydrocephalus are congenital causes, such as stenosis of the aqueduct of Sylvius or atresia of the foramina of Magendie and Luschka, tumors, intraventricular hemorrhages, infections, vascular pathologies, traumas. Prophylactic treatments are applied to the causes of hydrocephalus to prevent possible complications [3–5].

In intracranial space-occupying lesions, changes are observed in these intracranial structures. Not only the growth of intracranial space-occupying lesions, but also increases in intracranial blood volume/or cerebrospinal fluid lead to increases in intracranial pressure. Intracranial pressure increase usually causes headache, nausea, vomiting and bilateral papillary edema in patients. If patients with increased intracranial pressure are not treated,

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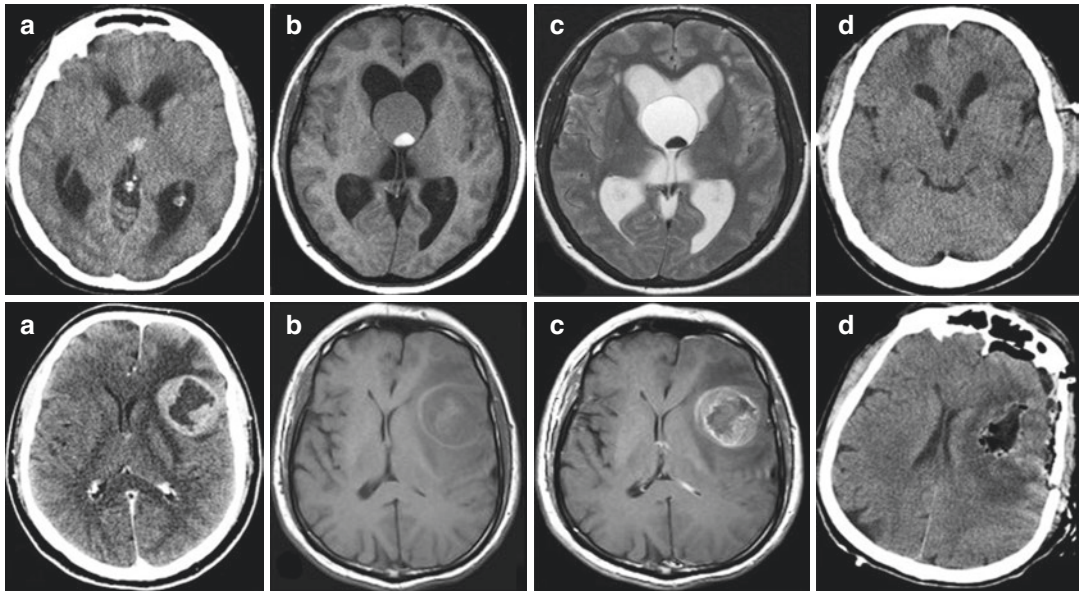

Fig. 34.1 *Top row*: Third ventricular colloid cyst causing acute hydrocephalus in a 36-year-old woman. The patient was brought to the emergency room with a loss of consciousness. CT scan (**a**) and T1- and T2-weighted axial MRIs with contrast demonstrate third ventricular colloid cyst causing acute hydrocephalus. The patient was operated on urgently. Her postoperative neurological examination was normal. Control postoperative CT scan was normal (**d**). *Bottom row*: Left frontal glioblastoma in a 55-year-old man. The patient presented with the complaints of headache and speech disorder that had been present for a month. In his examination, dysphasia was detected. CT scan (**a**), T1- and T2-weighted MRIs (**b**, **c**) examinations revealed a tumor in the left frontal that caused edema. Gross total tumor excision was performed. Postoperative CT scan (**d**) was normal. The patient's speech improved after the operation. Pathology examination confirmed gliobastoma. Radiotherapy and chemotherapy were performed

neurological deficits, and various herniation syndromes, which lead to changes in consciousness, develop [1, 2, 6] (Fig. 34.1).

34.3 Brain Tumors

According to the classification made by the World Health Organization, brain tumors are divided into seven subgroups: neuroepithelial tumors, tumors of the cranial-spinal nerves, tumors of the meninges, lymphoma-hematopoietic tumors, stretching-cell tumors, sellar tumors and metastatic tumors (Fig. 34.2). Approximately, 40% of brain tumors are glial tumors. While 60% of brain tumors in adults show supratentorial location, in children, the same rate is seen in the posterior fossa. Medulloblastoma is the most common malignant tumor in the posterior fossa that does not have a glial origin in children [7].

It is well known that low-grade glial tumors rise to higher-grade tumors (Fig. 34.2). Especially in diffusion and spectroscopic examinations using magnetic resonance imaging, preventive surgical interventions can be recommended to patients considering that there may be an increase in high-grade tumors in patients with low-grade glial tumors [8–10]. The same can be considered in benign tumors, such as meningioma (Fig. 34.3) [11]. Hemangioblastomas are life-threatening tumors that tend to bleed and grow [12].

Prophylactic surgeries are performed in patients with acromegaly (Fig. 34.4), Cushing disease and those who are not hormone secretaries, and who are at risk of vision loss with chiasm

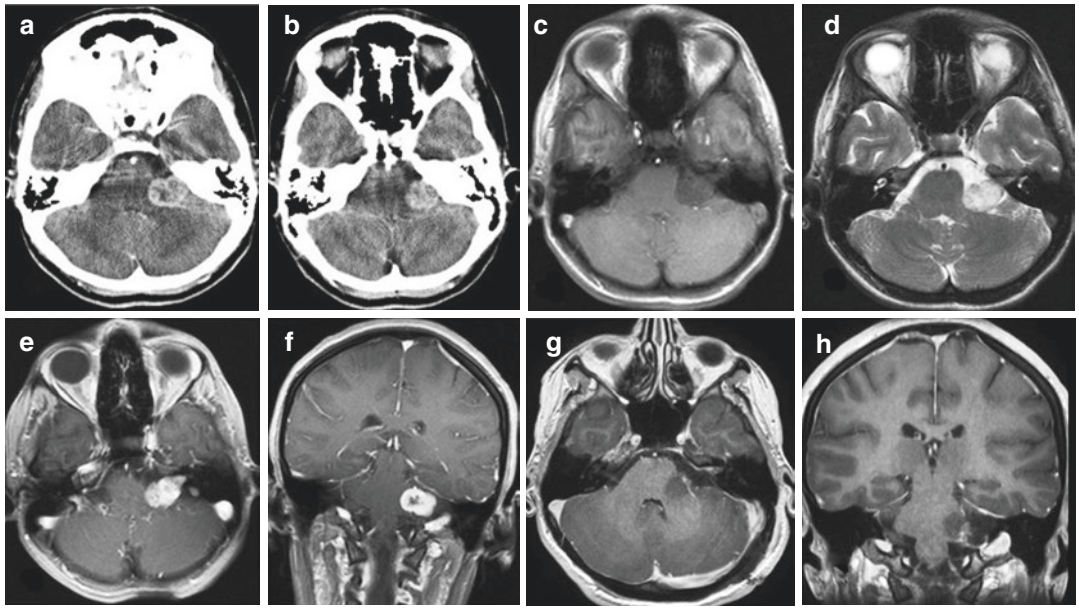

Fig. 34.2 Vestibular schwannoma of left pontocerebellar angle in a 23-year-old woman. The patient presented with numbness in the left face half. Neurological examination showed hypoesthesia in the left face half. Preoperative CT scan demonstrated a tumor in the left pontocerebellar angle (**a**, **b**). Preoperative T1- and T2-weighted MRIs (**c**, **d**) and T1-weighted axial and coronal MRIs with contrast (**e**, **f**) suggested a vestibular schwannoma in the left pontocerebellar angle. Total tumor excision was performed with the left rectosigmoid approach. The patient was very good postoperatively. Postoperative T1-weighted axial and coronal MRIs with contrast (**g**, **h**) confirmed total tumor excision. Histopathological examination confirmed the vestibular schwannoma

compression. In prolactinomas, if there is no chiasm compression, medical treatment should be considered first [13–17].

Metastatic brain tumors are mostly of lung carcinoma origin in men, while breast carcinoma origin is seen in women. In children, neuroblastoma, lymphoma and rhabdomyosarcoma are the causes of metastasis. In supratentorial single metastases and posterior fossa metastases, surgical treatment should be kept in mind to contribute to primary treatment [18, 19] (Fig. 34.4).

34.4 Cerebrovascular Diseases

Spontaneous subarachnoid hemorrhages (SAH) can lead to coma or even death. The incidence of SAH is between 4 and 20 per 100,000 per year. The rate of SAH from unruptured aneurysms is 1% per year. Aneurysms are the commonest cause of SAH, which may also result from a ruptured arteriovenous malformation (AVM), from a tumor or from a blood dyscrasia. Preventive surgical treatments are carried out especially for cerebral aneurysms, AVMs, cavernous angiomas, especially due to possible risk of bleeding (Figs. 34.5 and 34.6). Early diagnosis and prophylactic treatment play a very important role in reducing morbidity and mortality of patients due to aneurysm rupture. The main purpose of early diagnosis and prophylactic treatment is to prevent complications caused by aneurysm rupture and ischemia. Combining endovascular treatment and surgical treatment increases the success rate while reducing the complications, in the prophylactic treatment of AVMs. Since cavernoma can show both bleeding and growth, prophylactic surgical treatment can be performed especially to prevent the development of bleeding and neurological deficits [20–29].

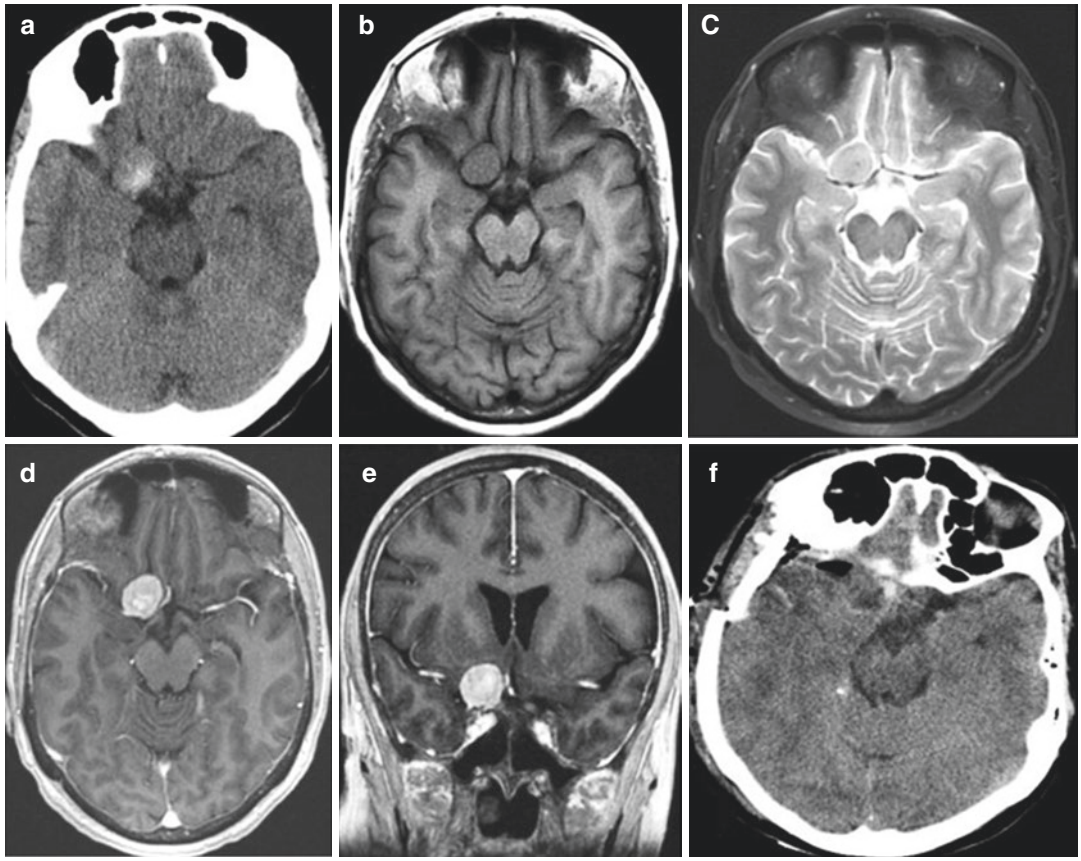

Fig. 34.3 Right anterior skull base meningioma in a 60-year-old woman. The patient presented with a headache. Neurological examination was normal. Preoperative CT scan (**a**) and T1- and T2-weighted MRIs (**b**, **c**) and T1-weighted axial and coronal MRIs with contrast (**d**, **e**) show a tumor at the right anterior skull base. Total tumor excision was performed. Postoperative period was uneventful. Postoperative control CT scan (**f**). There is no residue of the tumor. Histopathological examination revealed a meningothelial meningioma

34.5 Stroke

Over 80% of all first strokes are due to cerebral infarction. Only 10% of first strokes are due to hemorrhage primarily into parenchyma. The first hallmark of a stroke is its sudden onset. The second is the presence of focal symptoms and signs. When the focal sign happens to be a hemiparesis, the diagnosis of stroke may come to mind quite easily. For diagnosis of stroke, CT, MRI and DSA are the most important investigations. Both medical (antiplatelet agents, anticoagulants) and surgical treatments (carotid endarterectomy, bypass) should be considered to prevent the development of symptoms and signs due to stroke. Decompressive therapy may be necessary if intracranial pressure increase continues despite medical treatment [1, 30–32]. Prophylactic surgeries are important to prevent the development of ischemia in diseases that cause recurrent ischemia, such as moyamoya disease. For this purpose, direct revascularization operations should be considered (Fig. 34.7) [33].

34.6 Head Injury

Today, head injuries in, especially, children and young people are an important cause of morbidity and mortality. On the other hand, some head

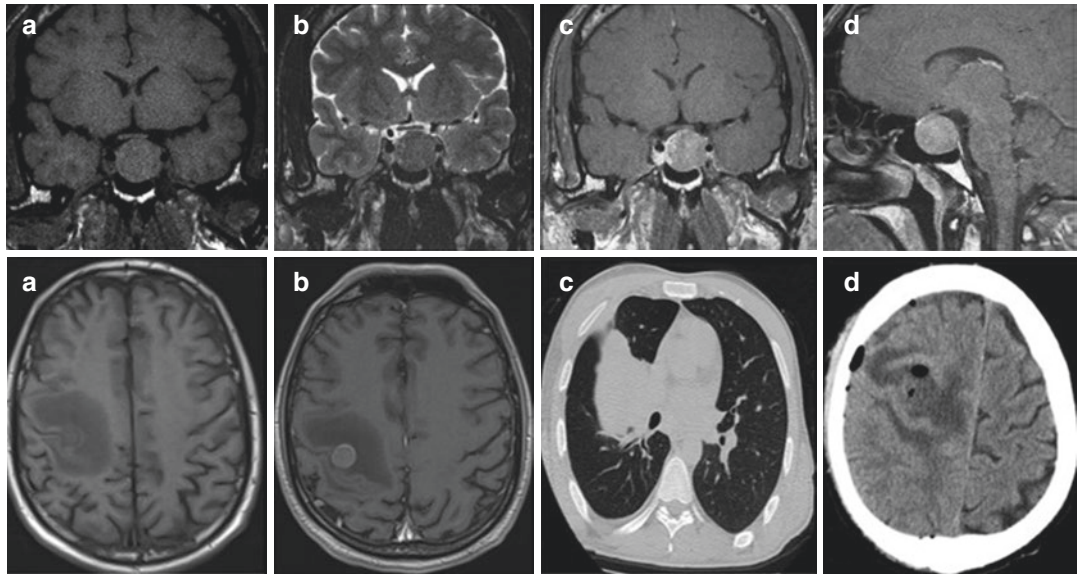

Fig. 34.4 *Top row*: Pituitary adenoma in a 41-year-old man. MRIs. The patient presented with the complaints of growth in his hands and feet, drinking too much water and urinating too much. Laboratory investigations revealed hyperglycemia, somatomedin-C (IGF-1) height and growth hormone height. Preoperative coronal T1- and T2-weighted without contrast (**a**, **b**) and coronal T1- and sagittal T1-weighted with contrast (**c**, **d**) MRI examinations show pituitary macroadenoma. A gross total tumor excision was performed with transsphenoidal endoscope-assisted surgery. There was no postoperative problem. *Bottom row*: Supratentorial single metastasis in a 36-year-old man with lung carcinoma. The patient was admitted with headache and left hemiparesis. Preoperative T1-weighted axial and T1-weighted axial with contrast MRIs (**a**, **b**) show a tumor in the right parietal. Preoperative thorax CT demonstrates a tumor in the right lung (**c**). Tumor was gross total excised. The patients's hemiparesis was improved in postoperative stage. Brain edema was decreased in postoperative CT scan (**d**)

injuries can lead to serious and life-threatening complications. For example, delays in patients with traumatic intracranial hematomas will lead to increased morbidity and mortality. Traffic accidents attract attention as the most common cause of head injuries. CT scan is the definitive radiographic study in the evaluation of head injury. It greatly improves diagnostic accuracy and facilitates management. In the early period following head traumas, brain damage may be caused by direct intracranial pressure increase, especially with hemorrhages, and brain damage caused by ischemia and hypoxia may also cause deterioration in patients. The management of head injuries is aimed at preventing secondary injury (Fig. 34.8). In patients who develop cerebrospinal fluid leaks after head trauma, dura repair and antibiotic treatment should be performed to prevent the development of meningitis [34–37] (Fig. 34.9).

34.7 Spinal, Spinal Cord and Peripheral Nerve Injuries

Spinal and spinal cord injuries are among the most important problems that can lead to the development of permanent neurological deficits. Preventive surgeries are of great importance for the prevention of permanent neurological deficits. In cases where neural tissue is preserved and deterioration occurs in the stabilization of the vertebrae, early diagnosis and prophylactic surgical stabilization are vital. In case of deterioration in the stabilization of the vertebrae, prophylactic surgery is also important in terms of stopping neurological deterioration if neural effects have begun (Fig. 34.10) [38–40].

Especially in peripheral nerve injuries that do not develop neurological deficits or are partially developed, good results can be obtained in case of early diagnosis and prophylactic surgical treatment [41].

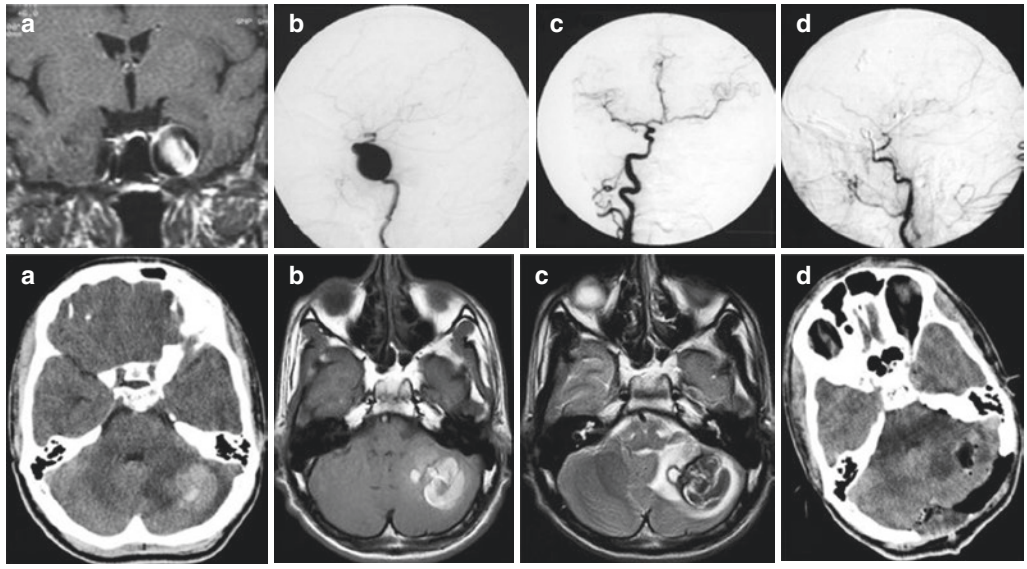

Fig. 34.5 *Top row*: Cavernous segment aneurysm of internal carotid artery in a 60-year-old man. The patient was admitted for 3 months with double vision. On neurological examination, there was restriction on the left side with ptosis and upward and downward gaze. Preoperative T1-weighted axial MRI with contrast (**a**) and DSAs (**b**, **c**) demonstrate cavernous segment aneurysm of the left internal carotid artery. The patient was operated under general anesthesia. Direct clipping was applied to the aneurysm. There were no problems after surgery. There is no aneurysm on postoperative DSA examination (**d**). *Bottom row*: Cerebellar cavernous angioma in a 16-year-old boy. The patient presented with headache, nausea and vomiting complaints. He had ataxia. Contrast-free brain CT examination shows a hematoma in the cerebellar hemisphere (**a**). T1- and T2-weighted MRIs demonstrate a acute hematoma (**b**, **c**). The patient was operated under general anesthesia. Vascular malformation with hematoma was excised in the operation. There was no problem after the operation. Histopathological examination confirmed a cavernous angioma. Postoperative CT scan was normal (**d**)

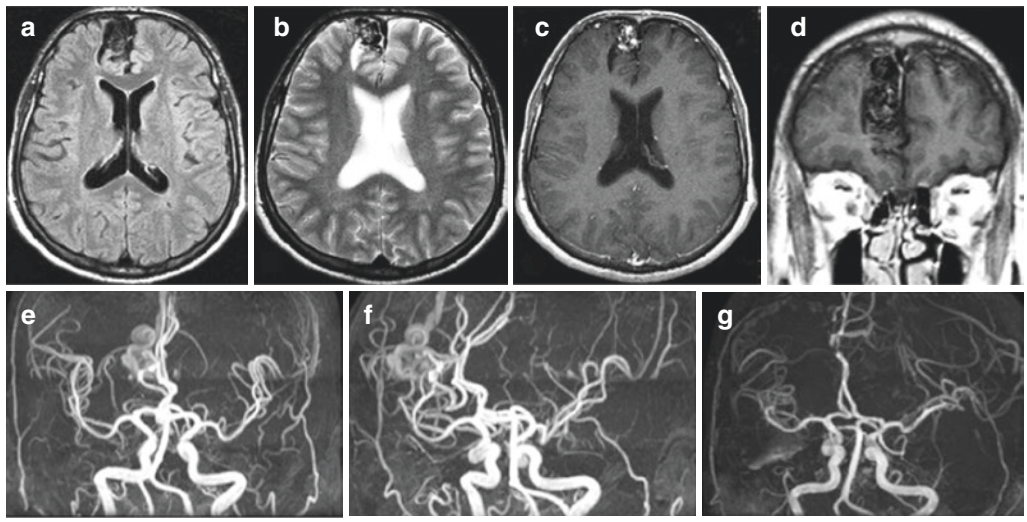

Fig. 34.6 Right frontal parasagittal AVM in a 34-year-old man. The patient presented with the complaint of headache. His neurological examination was normal. Preoperative T1- and T2-weighted axial MRIs without contrast (**a**, **b**) and T1-weighted axial, coronal MRIs (**c**, **d**) with contrast show AVM in the right frontal parasagittal location. Anteroposterior and oblique MRAs (**e**, **f**) reveal feeders from the distal anterior cerebral artery. Its drainage is in the superior sagittal sinus. The patient was operated under general anesthesia. Total AVM excision was performed. There were no problems after surgery. Postoperative MRA was normal (**g**)

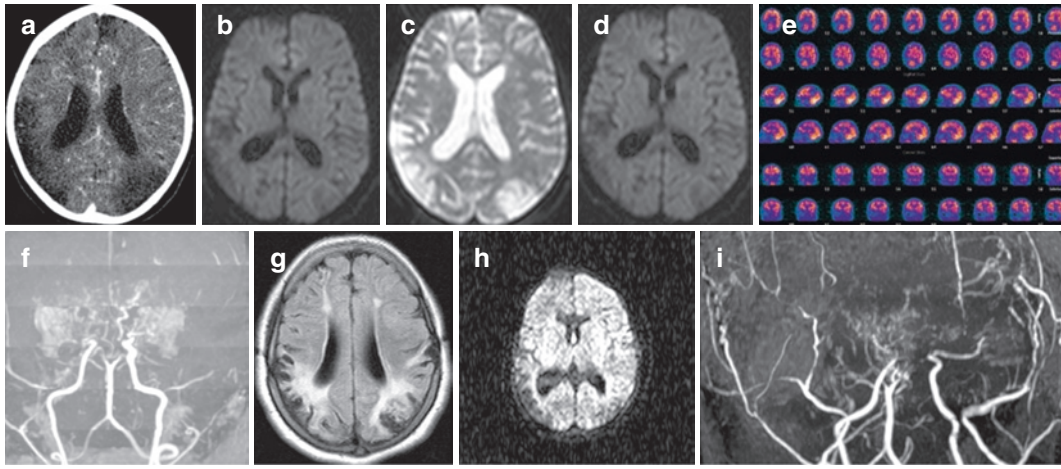

Fig. 34.7 Moyamoya disease in a 10-year-old girl. The patient presented with complaints of loss of strength in her arms and legs, and generalized seizures that did not pass with triple antiepileptic drugs. Her neurological examination revealed quadriparesis. Preoperative CT scan, T1- and T2-weighted axial and diffüzyon MRIs, SPECT and MRA views demonstrated total occlusion of ICA, neovascularization associated with bilateral parieto-occipitale infarct (**a**–**f**). Pial synangiosis surgeries were performed using the parietal branch of the external carotid artery on the right side and then on the left side with an interval of 9 months. There was no new finding in flair, diffusion and MRA examinations performed 1 year later (**g**–**i**)

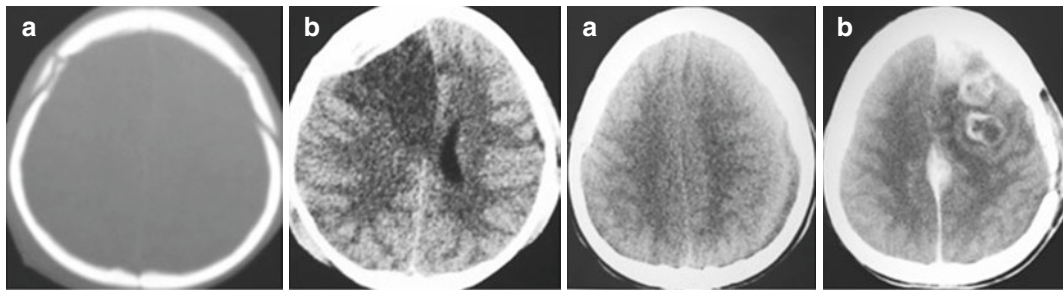

Fig. 34.8 Secondary ischemia following closed head trauma in 10-year-old boy. The patient was brought to the emergency room after a traffic accident. The patient was unconscious and had no lateralized signs. CT scan shows right frontal fragment fracture (**a**). Epidural hematoma and ischemia developed 2 days later (**b**). The hematoma was drained. Abscess in left hemisphere in 15-year-old female. The patient was brought to the emergency room after the fall. Skin incision and fracture were detected in the left parietal. The skin was sutured. The patient was given antibiotics. Intracranial surgical pathology was not detected in CT scan (**a**). After 15 days, intracerebral abscess developed in the left hemisphere (**b**). Abscess drainage was performed by surgical intervention. In the microbiological examination, *S. aureus* reproduced. Antibiotic treatment was applied for 8 weeks

34.8 Spinal Cord and Root Pressures

Spinal tumors can be classified into three groups based on their locations: extradural, intradural-extramedullary and intramedullary. Extradural tumors are most common, as they occupy the vertebrae body or structures outside the dura. They are most commonly metastatic. Intradural-extramedullary tumors are the second most common and come from the leptomeninges or nerve roots. These tumors are located inside the dura, but external from the spinal cord, as exemplified by meningiomas or neurofibromas [42, 43]. Ependymomas and astrocytomas are the most commonly encountered intramedullary spinal cord tumors, followed by hemangioblastomas [44–47] (Fig. 34.11). Tumors leading to spinal

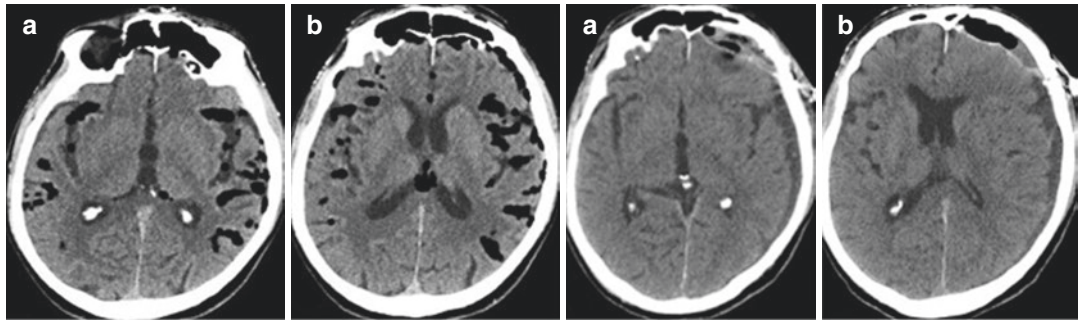

Fig. 34.9 Diffuse pneumocephalus in a 74-year-old patient. The patient was brought to the emergency room after falling from a height. Neurological examination of the patient was normal. There were headaches and rinore. CT scan shows diffuse pneumocephalus and fracture of the frontal sinus (**a**, **b**). The patient was operated. Both dura repair and frontal sinus repair were performed. Postoperative stage was uneventful. Control CT scans was normal (**c**, **d**)

cord compression are extradural malignant tumors in adult ages, while children have lymphoma, neuroblastoma and sarcomas [48]. Glial tumors, especially intramedullary astrocytoma and ependymoma and intradural-extramedullary meningioma and schwannomas, leading to spinal cord compression, can be without symptoms and signs. In patients with spinal cord compression, even if there are no symptoms or signs, prophylactic surgery should be performed to prevent permanent neurological deficits. Surgical interventions should be kept in mind in order to prevent permanent neurological deficits even in patients with spondylotic radiculopathy and myelopathies [49–52], together with intervertebral disc hernias that cause advanced compression [53–56].

34.9 Brain Abscess and Cerebral Hydatid Cyst

Brain abscess is a focal suppurative infection of the brain parenchyma. Its incidence is 1.3 per 100,000. They usually occur in the third and fourth decade. Brain abscess is more common in patients who have undergone bone marrow and solid organ transplantation, AIDS and neutropenic. Intracranial abscesses can be seen after a direct spread of a neighboring infection, such as the ears and sinuses, or a previous head injury. Brain abscess usually presents as a focal deficit. Abscesses caused by bacterial infections or lesions due to parasitic infections, such as hydatid cysts, can lead to increased intracranial pressure. Surgical treatment is applied in central nervous system infections due to the risk of neurological deterioration [57, 58].

Taenia Echinococcus causes hydatid disease. Cerebral hydatid cysts are mostly seen in children and young adults. The most common symptom is headache and vomiting due to increased intracranial pressure. Diagnosis can be made with CT scan and MRI (Fig. 34.12). It is important to remove the hydatid cysts without rupture [59, 60].

34.10 Congenital Hydrocephalus

Hydrocephalus is a common but complex condition caused by physical or functional obstruction of cerebrospinal fluid flow that leads to progressive ventricular dilatation. The incidence is 1 in 1000 births. Congenital obstructive or communicated hydrocephalus can be diagnosed by ultrasonography and magnetic resonance imaging in the prenatal period. Early diagnosis in the prenatal period facilitates prophylactic surgical interventions in the neonatal period or in infants without the emergence of neurological deficits. The main causes of congenital hydrocephalus are aqueductal stenosis, spina bifida (myelomeningocele) and Dandy-Walker

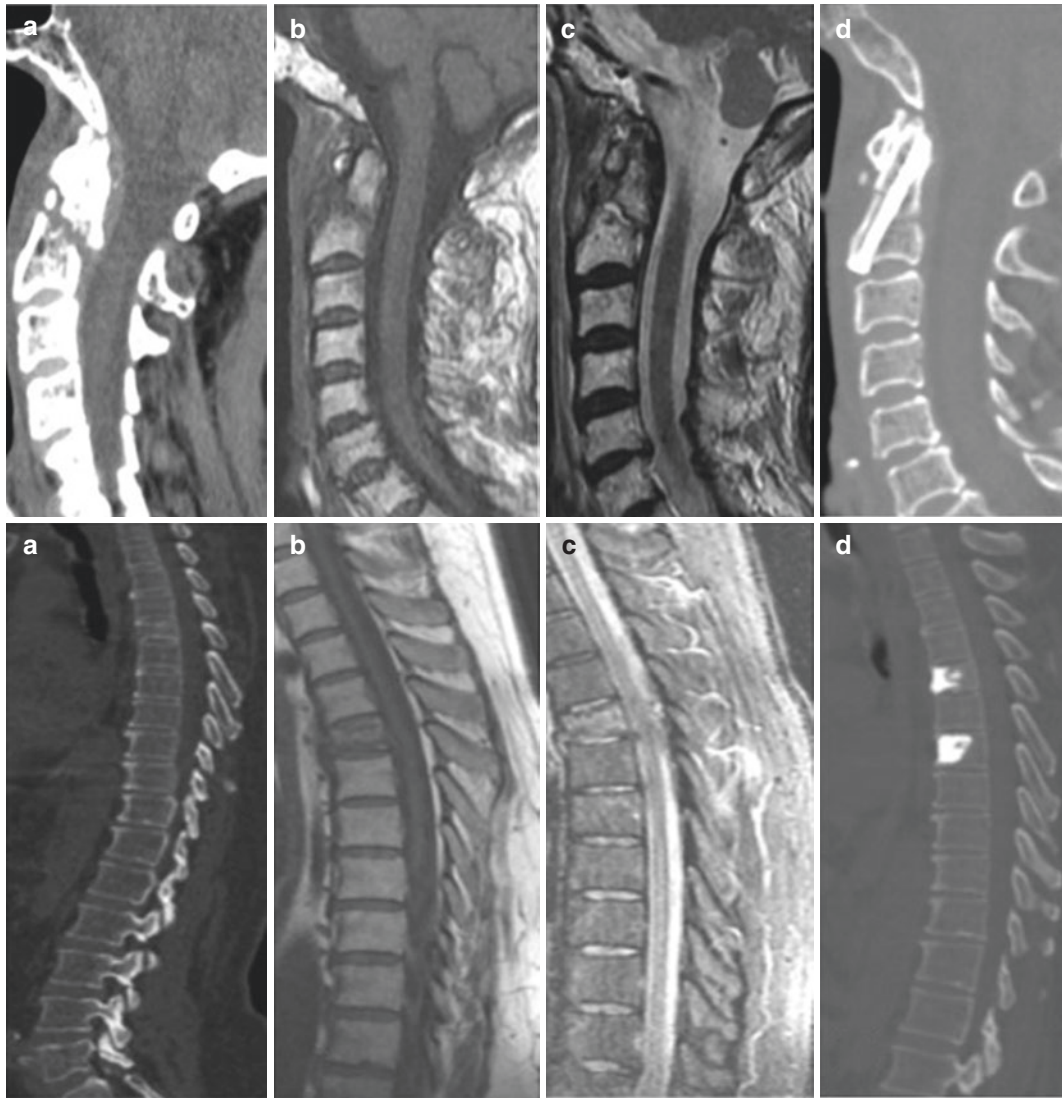

Fig. 34.10 *Top row*: Odontoid fracture in an 80-year-old woman. The patient presented with neck pain after falling. Her neurological examination was normal. Cervical T1- and T2-weighted sagittal MRIs and cervical sagittal CT scan examinations show the odontoid fracture in the second cervical spine (**a**–**c**). Odontoid fracture was fixed with screw. Control CT scan was normal (**d**). The patient was very well after the operation. *Bottom row*: Thoracic vertebral fractures in a 56-year-old man. The patient was admitted with post-fall back pain. His neurological examination was normal. Preoperative spinal CT scan (**a**), T1- and T2-weighted sagittal MRIs (**b**, **c**) show fractures of fifth and seventh thoracic vertebra. Images of kyphoplasty are seen in postoperative CT (**d**)

malformation. The most preferred surgical treatment method in congenital hydrocephalus is ventriculoperitoneal shunts. In addition, if intraventricular bleeding is detected during prenatal follow-up, ventriculosubgaleal shunts can be applied in the premature or neonatal period to prevent the development of hydrocephalus and neurological deficits (Fig. 34.13) [3–5, 61, 62].

34.11 Craniosynostosis

Craniosynostosis is the clinical condition that results from premature fusion of one or more sutures between the bones. Sagittal synostosis is the most common type of craniosynostosis and is most often seen in those who are nonsyndromic. Physical examination is very important in the

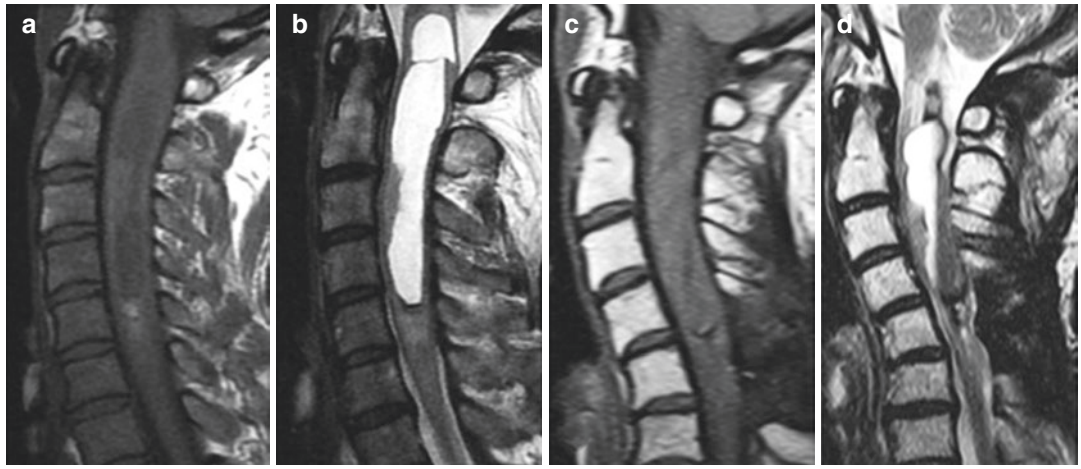

Fig. 34.11 Cervical intramedullary tumor in a 45-year-old man. The patient presented with a loss of strength in his arms for 15 days. Cervical T1- and T2-weighted sagittal MR examinations show the intramedullary tumor (**a**, **b**). Gross total tumor excision was performed. Histopathological examination confirmed the ependymoma. The patient was very well after the operation. There was no problem in control MR examinations (**c**, **d**)

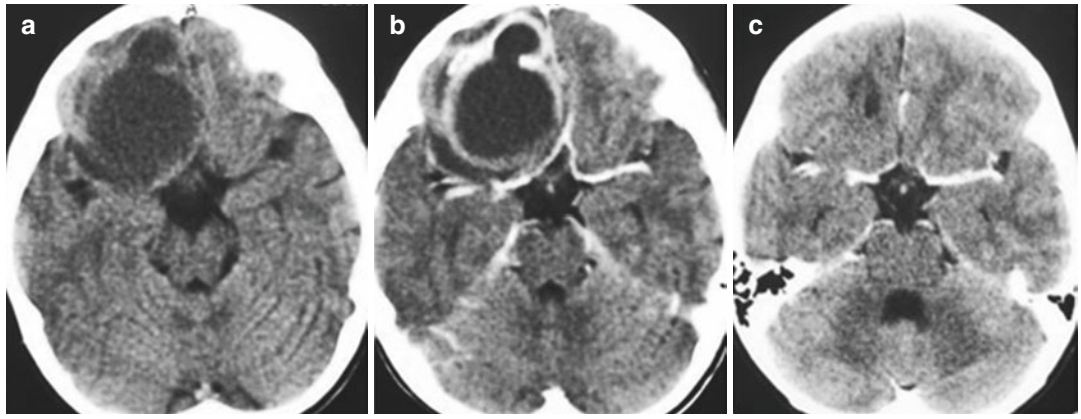

Fig. 34.12 Right frontal abscess in a 5-year-old girl. The patient presented with a headache complaint. She had no neurological deficit. Contrast-free and contrast-enhanced brain CT examinations show an abscess in the right frontal lobe, the content of which was hypodense and peripheral hyperdense (**a**, **b**). The patient was operated under general anesthesia. Right frontal burr hole was opened. Abscess was drained. There was no problem after the operation. *Staphylococcus aureus* was detected on the microbiological examination. Antibiotic treatment was applied for 6 weeks after the operation. There was no abscess in the control contrast-enhanced CT scan 3 months after surgery (**c**)

diagnosis of craniosynostosis. In new borns and infants diagnosed with craniosynostosis, prophylactic surgical intervention can be planned in the early months without any physical and neurological problems. In congenital diseases, such as tethered spinal malformation and tethered spinal cord syndrome diagnosed in the neonatal period or prenatal period, preventive surgical interventions should be performed without any neurological deficits (Fig. 34.14) [63–66].

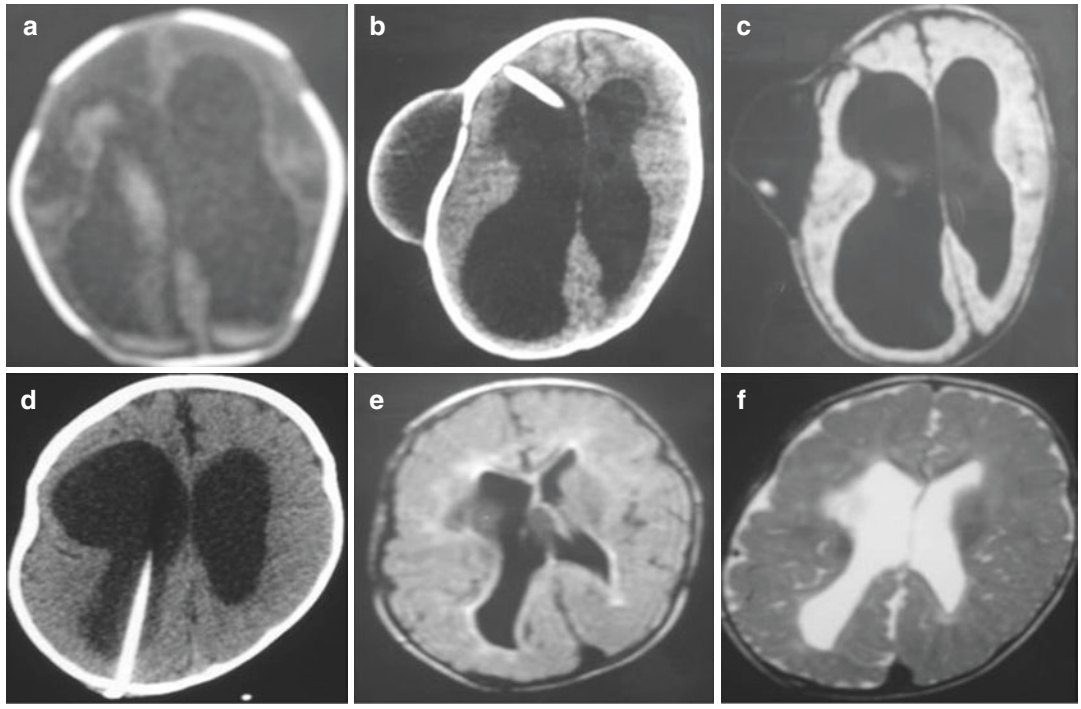

Fig. 34.13 Premature posthemorrhagic hydrocephaly in CT scan of 30th pregnancy month (**a**). Hydrocephaly was decreased after ventriculosubgaleal shunt (**b**, **c**). CT scan demonstrates a ventriculoperitoneal shunt 3 months after the ventriculosubgaleal shunt (**d**). There is no hydrocephaly in T1- and T2-weighted axial MRIs 12 months after the ventriculoperitoneal shunt (**e**, **f**)

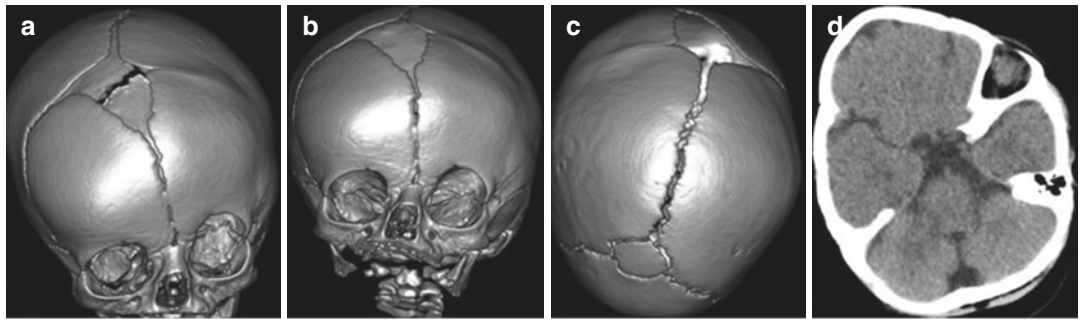

Fig. 34.14 Left coronal suture synostosis in a 3-month-old baby. The patient was brought due to a deformity in her head. 3D CTs and CT scan show left coronal suture synostosis (**a**–**d**).The patient was operated in 9-month-old. Bilateral linear craniectomies were performed parallel to the closed coronal suture

34.12 Meningocele, Myelomeningocele, Cranial Dysraphism

Meningocele is located in the midline on the spine. It is a cystic cavity formed by meningeal structures out of the spina bifida defect. There is a thin skin or membrane on the cyst. Embryologically, it is assumed to develop after the neurulation stage is complete. The majority of patients do not have neurological deficits. The purpose of prophylactic therapy is to prevent the

development of infection after rupture. In addition, cosmetic causes are indications for surgical treatment [67, 68].

Myelomeningocele is one of the most common serious congenital malformations. Myelomeningocele is an open spinal dysraphism, in which the spinal cord is not open as a result of neurulation defect. Its incidence is 1 in 1000 live births. The purpose of preventive therapy is to prevent the development of infection. However, postnatal surgery does not reverse or prevent the neurologic injury seen in myelomeningocele, reverse hindbrain herniation or prevent hydrocephalus. The neurologic defects result from primary incomplete neurulation and secondary chronic prenatal damage to the exposed neural elements through mechanical and chemical trauma [67, 69–71].

Cranial dysraphisms are rare congenital anomalies. The cranial meningocele contains meninges and cerebrospinal fluid in the skin-covered pouch. Encephalocele is a group of anomalies in which meninx, cerebrospinal fluid is protrude out of the calvarial and dural opening. The presence of gross brain tissue in the sac of encephalocele and the size of the sac are unfavorable factors for the prognosis. Encephaloceles divide into anterior and posterior groups. Posterior location is more common than anterior location. The aim of surgery is to repair the sac, maintain neural functions and maintain the cerebrospinal fluid circulation [72, 73] (Fig. 34.15).

34.13 Occult Spinal Dysraphism and Tethered Cord Syndrome

Open spinal dysraphism, such as meningocele and meningomyelocele, can be diagnosed more easily in the prenatal and early postnatal period. However, since closed spinal dysraphisms cause late clinical findings, radiological diagnosis can be made in the late periods. Early prophylactic surgical treatments without clinical findings provide very good results [74, 75].

Tethered cord syndrome (TCS) is a diverse clinical entity characterized by symptoms and signs, which are caused by excessive tension on the spinal cord. The majority of cases are related to spinal dysraphism. TCS can present in any age group, and presentations differ according to the underlying pathologic condition and age, with pain, cutaneous signs, orthopedic deformities and neurological deficits being the most common (Fig. 34.16). Surgical untethering is indicated in patients with progressive or new onset symptomatology. The surgical strategy aims to release the tethering structure, and thus the chronic tension on the cord. Early operative intervention is associated with improved outcomes [76–80].

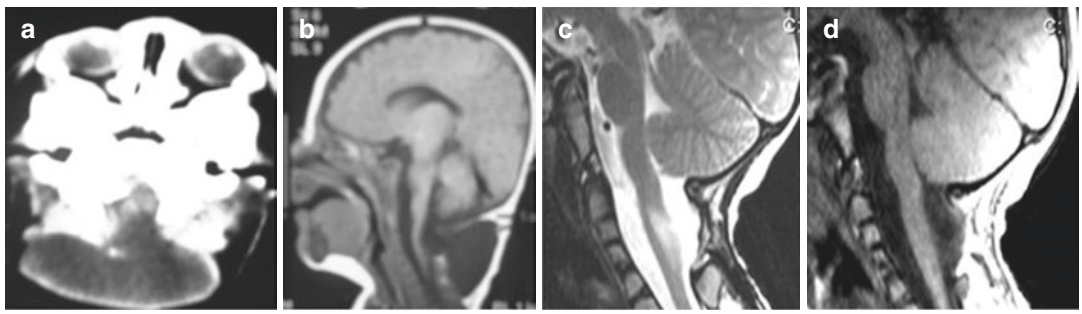

Fig. 34.15 Craniocervical meningocele in a 4-month-old baby. The patient was brought due to swelling in her neck. Neurological examination was normal. There was a craniocervical meningocele on physical examination. Preoperative axial CT scan and T1-weighted sagittal MRI show craniocervical meningocele of the patient (**a**, **b**). The patient was operated on general anesthesia. Meningocele was excised. Postoperative course was uneventful. Postoperative T2- and T1-weighted MRIs were normal (**c**, **d**)

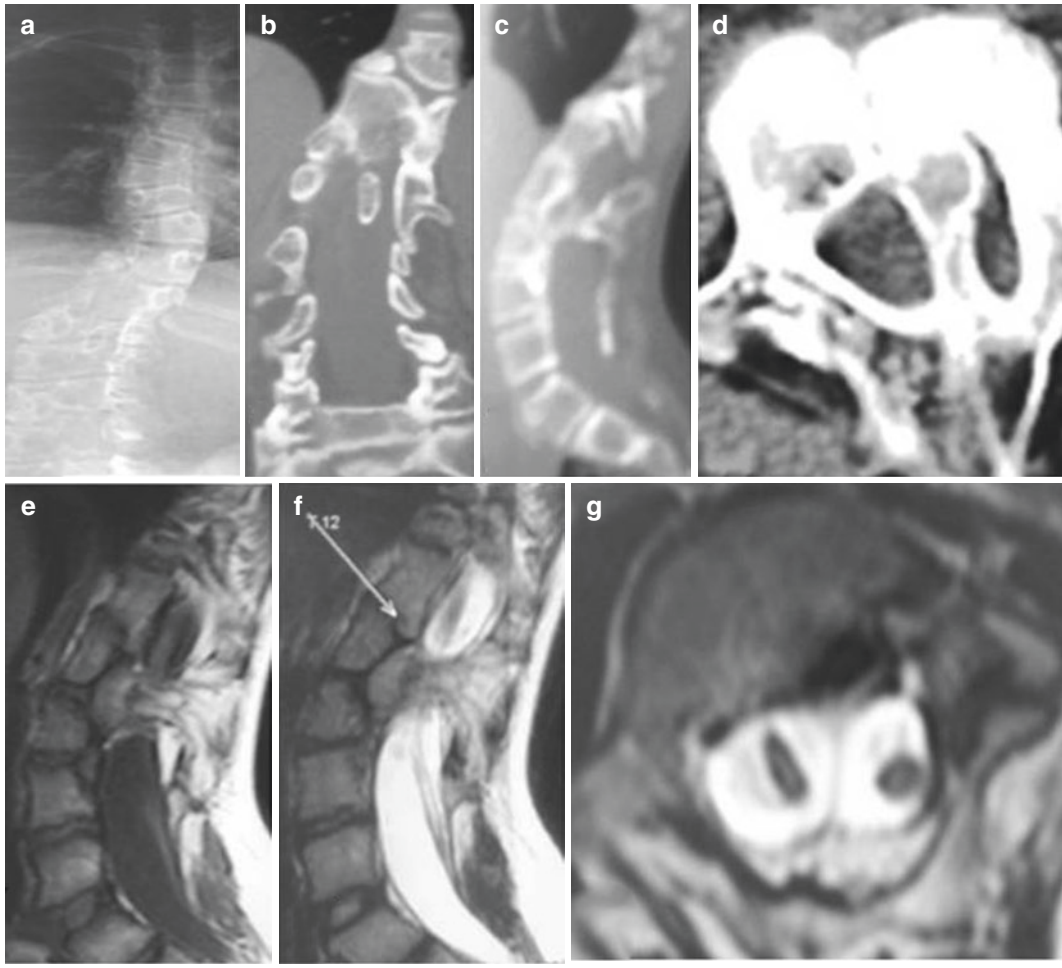

Fig. 34.16 SCM type I in an 11-year-old patient with scoliosis and TCS. Radiological examinations show scoliosis on preoperative radiograph (**a**), extradural spur on coronal, sagittal and axial CT examinations (**b**–**d**), interruption of the cord at the level of lumbar-1 on T1- and T2-weighted sagittal and T2-weighted axial MRI views (**e**–**g**). The patient was operated on under general anesthesia and in the prone position. Bone spur after laminectomy was explored at the level of lumbar-1. After the bone spur was excised, the double dura was exposed. The medial parts of both sides were opened. Medial dura sections were excised. Dura was planted to be one. Then, at the L4–5 level, the thick filum was explored and cut. The patient was very good after the operation. Subsequently, 3 months later, scoliosis surgery was performed by the orthopedic clinic

34.14 Dermal Sinus Tract

Dermal sinus tract is an epithelial-lined canal that leads to a potential union between the skin surface and deep tissues. It is a pathology showing congenital development. Cutaneous portion of the tract is visible as a midline dimple. Lumbosacral region is the most common place. In cranium, it is the occipital region. The incidence rate is 1 in 2500–3000 live births. MRI is essential to demonstrate both the extraspinal and intraspinal component of the dermal sinus tract (Fig. 34.17). If prophylactic surgery is performed before infection, TCS or neural compression, perfect results are obtained [81–85].

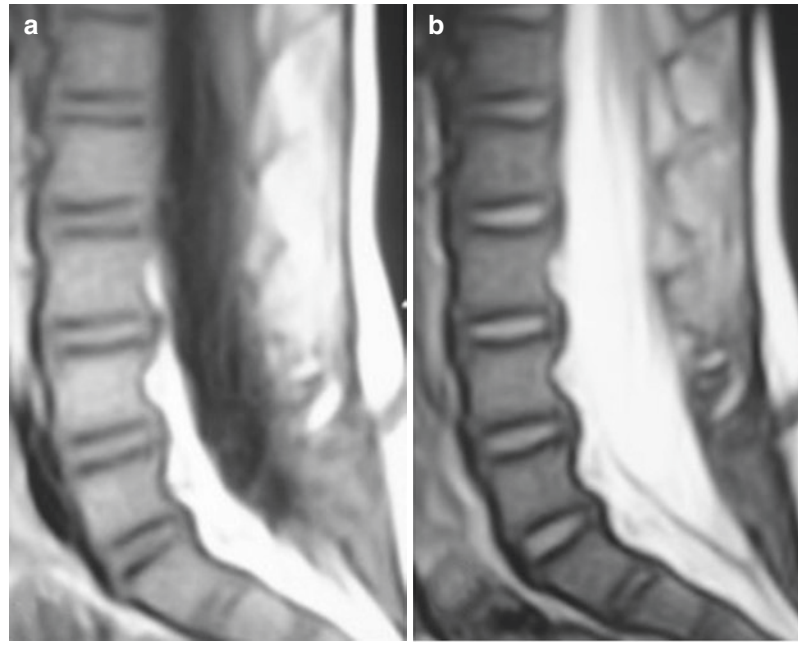

Fig. 34.17 Lumber dermal sinus tract in 2-year-old girl. The patient was admitted with lumber purulent pus. Neurological examination was normal. T1- and T2-weighted sagittal (**a**, **b**) MRIs show a dermal sinus tract of lumber midline. Dermal sinus tract was excised between skin and intradural distance. Postoperative period was uneventful

34.15 Spinal Lipomas

Lipomyelomeningoceles (spinal lipomas) are in the occult spinal dysraphism group. It is responsible for primary tethered spinal cord syndrome. The purpose of the treatment: It is the elimination of the pathology that causes stretching by preventing the movement of the spinal cord in the canal in the cranial direction. Thus, the spinal cord is released. The best results can be obtained with early preventive treatment surgeries (Fig. 34.18) [86–89].

34.16 Split Cord Malformation

Split cord malformation (SCM), also refered to as either diastematomyelia, double cord malformation or diplomyelia, is believed to occur due to a failure in gastrulation preceding neural tube closure. Pang et al. [90] suggested that SCM is caused by an ontogenetic error that occurs when the primitive neurenteric channel is closed. Dias and Walker [69] suggested that SCM developed from a failure of midline axial integration during gastrulation. SCM is a rare form of spinal dysraphism [74]. Type I SCM is a split cord, in which each hemicord lies within a separate dural tube, and a fibrous spur or a bony spur divides the spinal cord. Type II SCM refers to a split cord, in which the two hemicords are contained within a single dural tube, separated by a fibrous or cartilaginous tissue [90].

Many children with SCMs, especially when it occurs as an isolated pathology, are born with normal or nearly normal neurologic function. The most common skin finding is hypertrichosis. Other skin findings are hyperpigmentation, capillary hemangioma, dimple, dermal sinus tract, lipoma. Open spinal dysraphism may accompany. Orthopedic deformities, such as foot deformities, leg-length discrepancy, pes cavus, talipes equinovarus, pes planus, scoliosis, kyphoscoliosis, are quite common. SCM is seen in approximately 5% of patients with congenital scoliosis or kyphoscoliosis. Radiological procedures used for the diagnosis of SCM are spinal X-ray, ultrasound, CT scan, myelo-CT and MRI (Fig. 34.19). In addition to scoliosis, spina bifida, vertical laminar fusion,

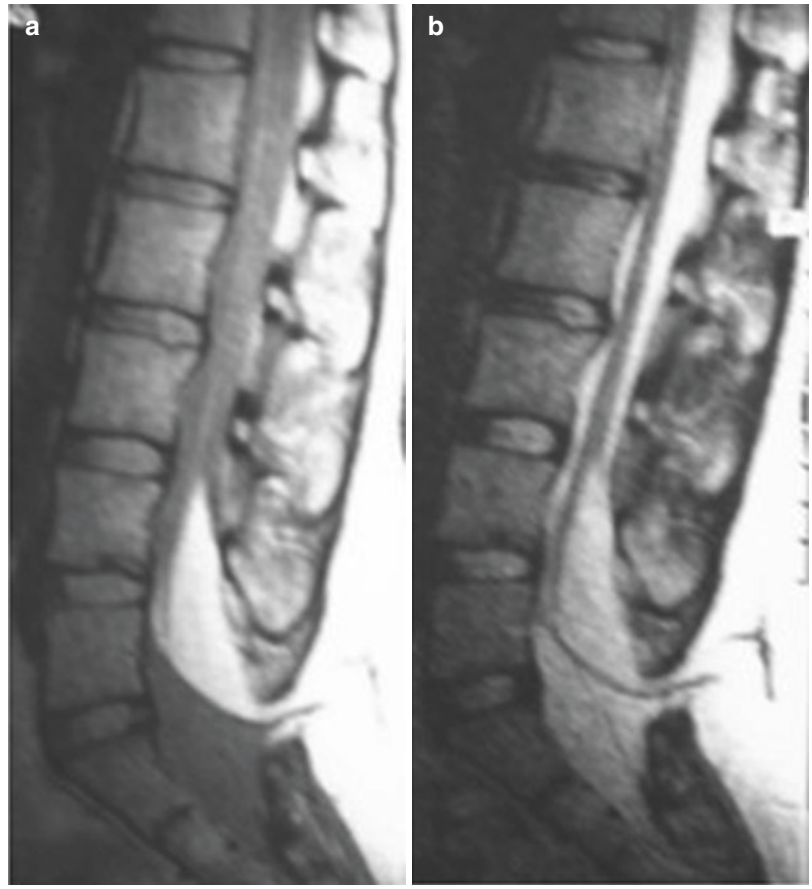

Fig. 34.18 Lumber lipomyelomeningocele in a 25-year-old woman. The patient presented with low back pain. Neurological examination was normal. Spinal T1- and T2-weighted MRI examinations showed lumber intradural lipoma (**a**, **b**). Spinal cord was released by removing the lipoma with prophylactic surgery. There was no problem after the operation

fused vertebral bodies, split vertebral body, scoliosis, kyphoscoliosis, fused or deformed spinous processes, bifid lamina, block vertebra, butterfly vertebra and accessory lamina can be detected in direct vertebral radiographs. Before MRI, myelography and CT myelography were successfully used. Three-dimensional CT is especially useful in imaging of type I malformation and accompanying scoliosis. With the widespread use of MRI, there has been an increase in SCM diagnoses. While MRI provides detailed information about SCM, it also provides detection in concomitant pathologies, such as hydromyelia. Ultrasonography helps diagnosis during intrauterine and newborn periods. In the preoperative period, somatosensory-evoked potentials and urodynamic studies should be performed. This can be useful for follow-up periods. The most common level of septum is lumbar and thoracolumbar vertebrae. It is rarely seen in the cervical region. It is usually associated with Klippel-Feil syndrome. The degree of scoliosis increases with advancing age. Prophylactic surgical treatment is recommended before neurological symptoms, and signs appear in patients with SCM. Prophylactic surgical treatment provides very good results. Surgical complication is very low [91–103].

34.17 Chiari Malformation

Chiari malformations (CMs) represent a group of anomalies characterized by descent of the cerebellar tonsils or vermis into the cervical spinal

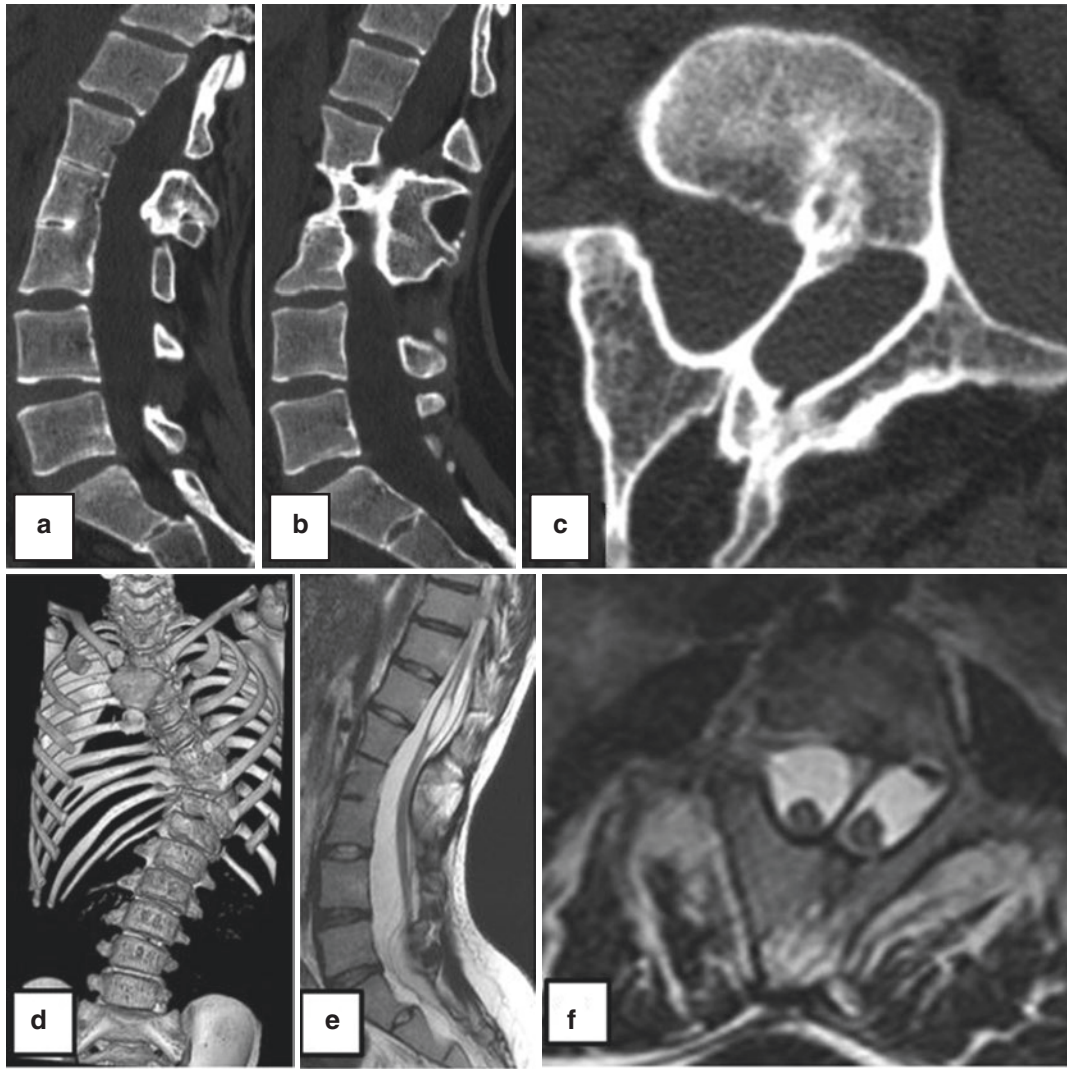

Fig. 34.19 Scoliosis and syringomyelia in a 17-year-old patient with SCM type I. Spinal sagittal and axial CT scans (**a**–**c**) and three-dimensional (3D) CT examination (**d**) demonstrate spinal fusion at the L1, L2, L3 levels (**a**), bone spur at the L2 level of SCM type I (**b**, **c**), thoracolumbar scoliosis (**d**). T2-weighted sagittal and axial MRIs show syringomyelia at the thoracal-12 level (**e**), double spinal canal of SCM type I (**f**). Prophylactic surgical intervention for type I SCM was performed. Postoperative period had no problems

canal. Chiari type I malformation is a congenital hindbrain anomaly characterized by downward displacement of the cerebellar tonsils through the foramen magnum. Chiari type I is the most common CM. It is estimated to occur in approximately every 1 in 1000 births. This is an adult type and tends to be diagnosed in the second or third decade of life. The most common clinical symptom is headache, especially localized in the suboccipital region. The most accompanying pathology of CM is syringomyelia (Fig. 34.20). Type II is an associated meningomyelocele. Type III has the features of type II with an additional herniation of the entire cerebellum through the bony defect involving the foramen magnum, forming an encephalocele. Type IV is a form a cerebellar hypoplasia. The most valuable diagnostic methods for diagnosis are MRI and CSF

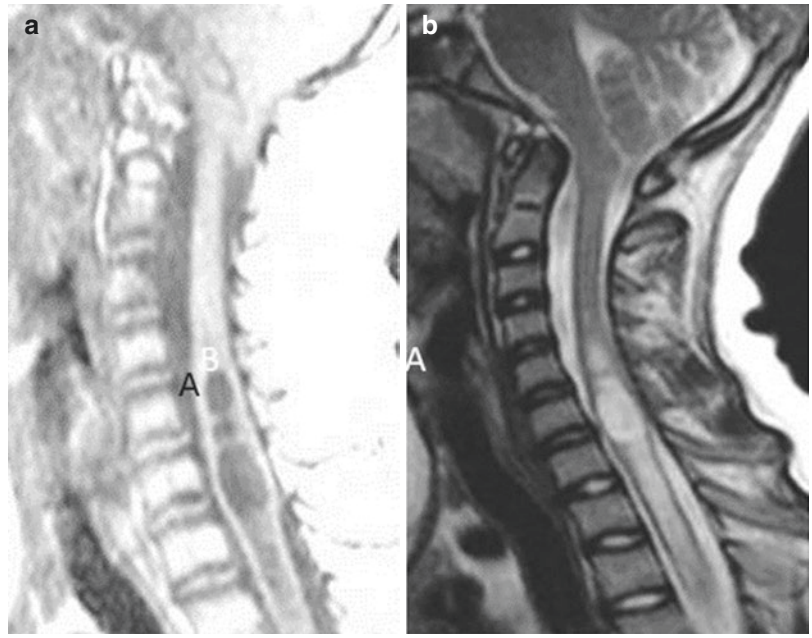

Fig. 34.20 CM and syringomyelia in a 6-year-old male. The patient was admitted due to headache. Neurological examination was normal. Preoperative T1- and T2-weighted MRI examinations (**a**, **b**) show Chiari type I malformation associated with cervical syringomyelia. Craniocervical decompression and duraplasty were performed in the prone position under general anesthesia. He had no problems after surgery

flow MRI. The commonly used method in the treatment is craniocervical decompression and duraplasty. Preventive surgical treatment without developing clinical findings provides very good results [104–108].

34.18 Arachnoid Cysts

Arachnoid cysts are the most common intracranial cysts and make up 1% of all intracranial space-occupying lesions. We can divide arachnoid cysts into congenital and acquired arachnoid cysts. Congenital (real) arachnoid cysts are formed during the early embryonic formation of the primitive arachnoid membrane. Acquired arachnoid cysts develop as a result of trauma, hemorrhage, chemical irritation, tumor or inflammatory events after the cerebrospinal fluid is trapped in the arachnoid scar tissue. They can be asymptomatic, as well as cause headache, vomiting, hydrocephalus findings, endocrinological disorders, focal neurological findings, seizures and cerebellar findings in posterior fossa cysts. Arachnoid cysts that tend to be symptomatic are treated with prophylactic surgical treatment methods [109–114] (Fig. 34.21).

34.19 CyberKnife Radiosurgery for Brain Tumors

CyberKnife radiosurgery can sometimes be applied as an additional treatment option in both benign and malign brain tumors. It can be preferred for tumors with critical localization and less than 3 cm in size. Vestibular schwannomas, meningiomas, pituitary adenomas, primary and metastatic malign brain tumors are the most preferred brain tumors in CyberKnife radiosurgery [115–131] (Fig. 34.22). In addition to brain tumors, CyberKnife radiosurgery is used as the primary or additional treatment in the treatment of cerebral AVMs [132, 133].

34.20 Conclusion

The prophylactic surgical treatment results in neurosurgical diseases are usually good if appropriate patient selection is made. The number of neurosurgical diseases that can be planned for prophylactic surgery is many. Prophylactic surgical treatment should be planned without delay after diagnosis in cerebral aneurysms, tumors, hydrocephalus, congenital and degenerative diseases that have a severe pressure effect on neural tissues.

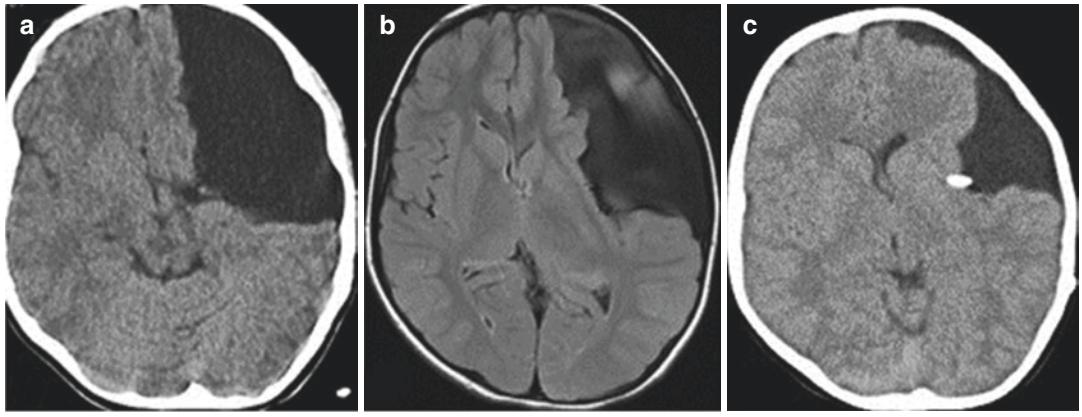

Fig. 34.21 Left frontoparietal arachnoid cyst in an 11-year-old girl. The patient presented with a headache complaint. Neurological examination was normal. Preoperative CT scan (**a**) and T1-weighted axial MRI (**b**) examinations demonstrate a arachnoid cyst in the left frontotemporal localization. A cystoperitoneal shunt was placed in the patient under general anesthesia. The patient was good after the operation. Arachnoid cyst was smaller in the CT examination 3 months later (**c**)

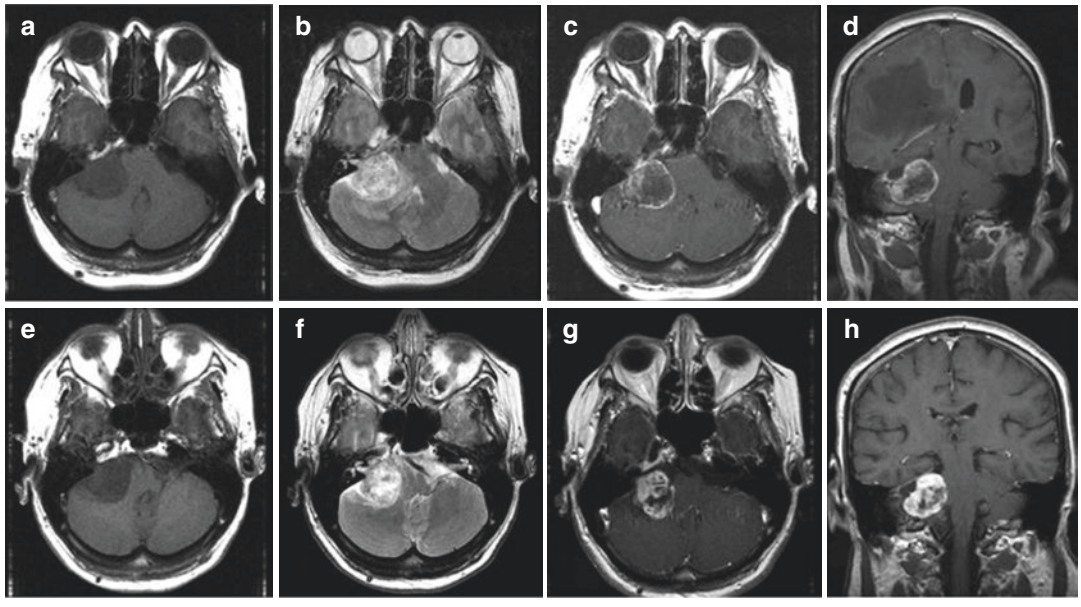

Fig. 34.22 Right vestibular schwannoma in a 60-year-old woman. The patient was admitted with hearing loss on the right side for 4 years. T1- and T2-weighted axial MRIs, and T1-weighted axial and coronal with contrast MRIs show a vestibular schwannoma in the right side (**a**–**d**). The patient preferred CyberKnife radiosurgery. Control MRI examinations are seen 15 months later (**e**–**h**). Significant reduction in tumor size is not yet observed

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Prophylactic Procedures for Orthopedic Pathologies

35

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35.1 Introduction

Orthopaedics and traumatology encompasses many subspecialities involving pediatric orthopedics, orthopedic oncology, hand surgery, foot and ankle surgery, traumatology, deformity management, sports medicine, and arthroplasty. In this chapter, we aimed to give a brief information for some prophylactic procedures in orthopedics, which may be useful not only for orthopedic surgeons, but also to other doctors to have a general idea for referring their patients and adequately addressing their problems. Timely implementation of prophylactic procedures may decrease the patient's morbidity and even mortality, especially in oncological cases. For example, simple treatment of developmental hip dysplasia in infancy with pelvic harness may prevent formidable hip arthroplasty in early adulthood, or prophylactic fixation of an impending fracture in a patient with bone metastases may improve patient survival substantially. Simple prophylactic exostectomy for small diabetic foot ulcer may prevent an unnecessary amputation in future. In this context, three main topics were selected for prophylactic surgery in orthopedic pathologies, including pathological fractures, foot and ankle problems and osteoarthritis of knee and hip, and developmental hip dysplasia.

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35.2 Prophylactic Surgery to Prevent Pathologic Fractures

A fracture that develops through an area of bone pathology is termed as a pathologic fracture. When the extent of bone destruction is such that a bone can no longer withstand physiologic loads and a fracture is imminent, it is termed as an impending fracture. Pathologic fractures can be secondary to a benign lesion, such as Paget disease, giant cell tumor of bone, hemangioma, or a malignant tumor, which may be a primary bone or hemopoietic malignancy (osteosarcoma, chondrosarcoma, lymphoma, multiple myeloma) or metastatic carcinoma.

The common solid tumors that metastasize to the bone arise from breast, prostate, kidney, lung cancer, or thyroid gland [1]. Metastases to bone develop in about two-thirds of all patients who die from cancer [2]. Involvement of bone is seen

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in <95% of patients with multiple myeloma, 75% of patients with breast and prostate cancer, and 15–40% of patients with other types of tumors [3]. The most common origin of bone metastasis due to a solid organ is breast carcinoma in women and prostate carcinoma in men. Skeletal lesions can be also the first manifestation of malignancies in 25–30% of solid organ tumors. Bone metastasis can also develop in patients with osteosarcoma, chondrosarcoma, and Ewing's sarcoma; however, soft tissue sarcoma rarely causes bone metastases. Pain, pathologic fracture, hypercalcemia, and spinal cord compression are forms of skeletal-related events (SREs) due to bone metastases [4].

Multiple myeloma is another frequent cause of the pathological fracture. It is characterized by a malignant monoclonal proliferation of plasma cells. It is the second most common hematological malignancy after non-Hodgkin's lymphoma and the most common primary bone tumor in older patients. In multiple myeloma bone disease, the interaction between malignant plasma cells and bone microenvironment leads to increased osteoclastic function with decreased osteoblastic activity. Twenty-five percent of the patients present with spontaneous fracture, and the death rate is increased by more than 20% in these patients with pathological fractures. Stavropoulous et al. found that the patients presenting with a spontaneous fracture at diagnosis had poorer prognosis with median overall survival of 30 months compared to 86 months in those without fractures. The risk of death was also significantly increased in patients who developed all subtypes of fracture after multiple myeloma. Prophylactic fixation before complete fracture occurrence, therefore, is an important treatment strategy in these patients.

The goals of treatment, regardless of underlying etiology, are to minimize morbidity and maximize function and skeletal integrity. For most patients with a completed or impending pathologic fracture of a long bone, this will necessitate surgical fixation. Surgical treatment of impending fractures is technically easier and less morbid compared to surgical treatment of complete pathological fractures. In various studies, surgical fixation of impending fractures due to metastatic bone disease has also demonstrated improved longer survival in comparison to complete pathological fractures. The improved survival could be attributed to the fact that fixation of impending fracture bears advantages of less morbidity, which results in correspondingly low secondary surgical complications, such as infection, implant failure, and venous thromboembolism, among others. It also contributes toward the timely initiation of chemotherapy or radiation treatment for these patients.

The diagnosis of impending or complete pathological fracture is established on radiographic studies. With advances in imaging technologies, such as whole-body-magnetic resonance imaging (MRI), positron emission tomography-computed tomography (PET-CT) allows for whole-body screening with high sensitivity and specificity. This has enabled early diagnosis of impending fractures in asymptomatic patients and treatment with radiation therapy with or without early surgical fixation.

One of the most common scoring systems used in decision-making in a metastatic extremity lesion is Mirels' classification. It is based on four characteristics. It takes into account the site of the lesion (upper limb/lower limb/trochanteric region), nature of the lesion (blastic/mixed/lytic), size of the lesion, and presence of pain. Points are allocated as shown in Table 35.1. The scoring

Table 35.1 Mirels' scoring system

Site of lesion	Score
• Upper limb	1
• Lower limb	2
• Trochanteric region	3
Nature of lesion	
• Blastic	1
• Mixed	2
• Lytic	3
Size of lesion	
• 1/3 of cortex	1
• 1/3–2/3 of cortex	2
• >2/3 of cortex	3
Pain	
• Mild	1
• Moderate	2
• Functional	3

Table 35.2 Treatment recommendations according to Mirels' score

Mirels' score	Treatment recommendation
≤7	Radiotherapy and observation
8	Use clinical judgment
≥9	Prophylactic fixation

system suggests a treatment algorithm based on the total score (Table 35.2).

Lesions in the pertrochanteric area are at the highest risk of fracture due to maximal stresses on this part of the femur on load-bearing. For scores ≤7, the lesion can be treated conservatively with radiotherapy and observation. For a score of ≥9, prophylactic fixation is recommended. The overall score of eight presents a clinical dilemma. The probability of fracture is only 15%, and Mirels' recommended the treating attending physician to use clinical judgement in such cases in considering prophylactic fixation [5].

Precise estimation of survival in patients with metastatic disease is of utmost importance and allows for treatment planning for patients who present to healthcare facilities with impending or complete pathological fractures. Treatment modalities vary depending on estimated survival, and PathFx model is a new promising prediction model, taking into consideration age, gender, type of pathological fracture, presence of visceral metastasis, lymph node metastasis, hemoglobin and leukocyte concentration at initial presentation, primary oncological diagnosis, number of bone metastasis, and ECOG status of the patient. It has been validated in various populations [6, 7].

For solitary lesions, a different treatment strategy is recommended, especially if the metastatic lesion is arising from renal cell carcinoma (RCC) or thyroid carcinoma. In these lesions, wide surgical resection compared to surgical fixation is important, as it is related to improved survival and even complete cure of the disease in some cases. The decision is made jointly by an orthopedic oncologist, medical oncologist, and radiation oncologist.

The impending pathological fractures of the extremities can be treated using orthopedic plates or intramedullary (IM) nails (Figs. 35.1 and 35.2). Plate fixation offers a load-bearing construct, whereas intramedullary nailing works a load-sharing construct. Where feasible, IM nailing is preferred as it is as a load-sharing device, is possible to be performed closed (without opening up the site fracture or pathology), and has the advantage of spanning most of the length of the long bone, thereby preventing the need for further intervention should a subsequent lesion develop in the same bone.

The aim of radiotherapy in patients with bone metastasis is to improve the quality of life, maintain skeletal function, and minimize pain. Radiotherapy, as a treatment modality in patients who have metastatic lesions of the long bone, should be planned according to the Mirels' scoring system [5]. Radiotherapy in patients with bone metastasis aims to improve the quality of life, maintain skeletal function, and minimize pain. Radiotherapy enables to destroy tumor cells and, therefore, provides a suitable environment for potential union. Apart from being the basic modality of treatment for patients with Mirels' score of 7 or under, radiotherapy is also utilized in an adjuvant manner following stabilization of a complete or impending pathological fracture in a patient with Mirels' score of 9 or more (Table 35.1).

With improvements in chemo and radiotherapy, surgical fixation techniques with newer reliable implants decreased surgical complications. It is possible to improve the overall quality of life for patients with impending and complete pathologic fractures. The orthopedic surgeon treating the patient must be aware of compromised healing characteristics of pathologic bone along with increased infection rates in these patients due to underlying tumor processes and related treatment. Where possible, an orthopedic oncologist should be involved in the care of such patients. The ultimate goal is to obtain immediate functional recovery and strategies to allow for appropriate adjuvant treatments to improve the overall quality of life in these patients.

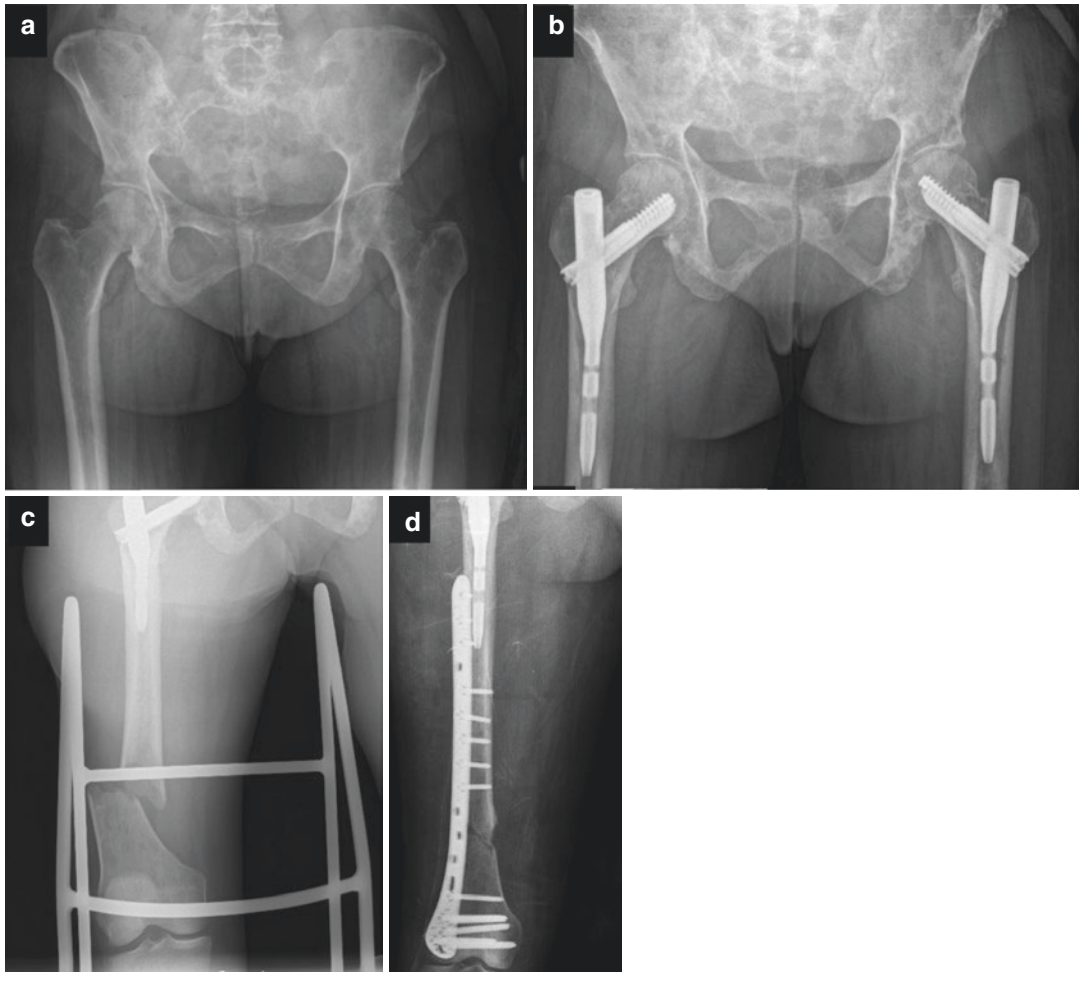

Fig. 35.1 The 44-year-old woman with bilateral impending proximal hip fracture due to metastatic breast carcinoma (**a**) preoperative view. (**b**) After implementation of bilateral proximal femoral nails. (**c**) At 6 months after surgery, this time complete fracture at the distal femoral diaphysis, (**d**) plate fixation was performed

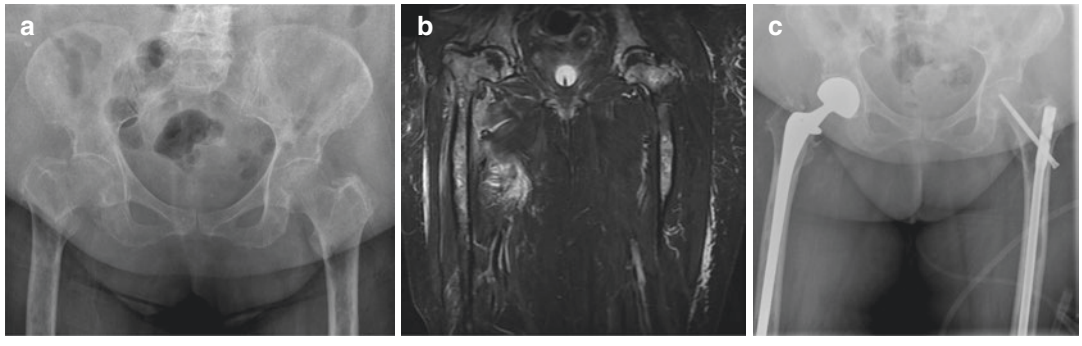

Fig. 35.2 The 84-year-old woman with right complete fracture and left impending fracture due to metastatic breast carcinoma (**a**) preoperative radiograph. (**b**) Preoperative MRI. (**c**) Long-cemented prosthetic replacement to the right hip and long reconstruction nail fixation on the left femur

35.3 Prophylactic Surgery in Foot and Ankle

The foot is a unique structure designed to withstand significant loads. It is, thus, imperative that preoperative planning plays a significant role in foot and ankle surgery. When a surgeon performs an osteotomy or a tendon surgery, the biomechanics of the foot are altered. The foot is unique in that it molds as it is squeezed into a shoe. The bony prominences, minimal subcutaneous tissue, and presence of any implants in a foot may contribute to persistent pain. There are certain circumstances where prophylactic surgery for the foot and ankle is indicated.

In hallux valgus surgery, the metatarsal parabola needs to be restored intraoperatively. When shortening osteotomies of the first metatarsal are performed, the lesser metatarsals may remain relatively longer. This consideration should be included in the preoperative plan, and intraoperatively lesser metatarsals may need shortening to prevent formation of callosities and pain under the second (or third) ray (Fig. 35.3a–c). Likewise, in patients with hallux rigidus undergoing first metatarsophalangeal arthrodesis, it is recommended that the interphalangeal sesamoids (if present) be excised to prevent late symptoms [8].

Patients with peripheral neuropathy or Charcot foot have significant issues with wound healing and are at high risk for developing decubitus ulcers [9]. In such patients, prophylactic exostectomy to remove bony prominences assists not only with wound healing, but also in the prevention of ulcers and should be considered.

It is not uncommon to have patients complain of hardware-related symptoms in the foot and ankle as discussed earlier. They may complain of prominent plates or screw heads making shoe wear uncomfortable. Implant removal may also be considered as prophylactic surgery in these circumstances. In clinical practice, some surgeons routinely advise implant removal to their patients.

35.4 Prophylactic Surgery to Prevent Knee Osteoarthritis and Pain

Osteoarthritis in the knee joint (gonarthrosis) develops due to the joint cartilage damage caused by injury to the joint cartilage or improper distribution of forces on the joint because cartilage functions as a weight-bearing layer and absorbs and distributes loads to the underlying bone [10]. The nonuniform distribution of loads on cartilage is the most common pathology causing primary osteoarthritis in the human knee, and the development of osteoarthritis can be prevented, delayed, or even partially cured by prophylactic surgical methods. Prophylactic restoration of the anatomy aims to preserve the biological vitality of the patient's tissues as much as possible rather than changing them to prosthe-

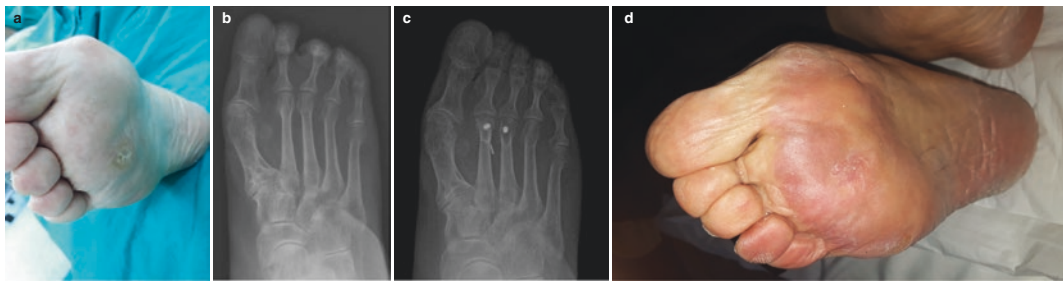

Fig. 35.3 The 57-year-old female patient was complaining metatarsalgia under the second and third ray of the foot. Painful callosities were observed (**a**). She underwent an osteotomy due to hallux valgus deformity 8 years ago. Relatively long metatarsals (marked with asterix) were seen at her foot anteroposterior radiograph, which is considered to be the reason for the pain (**b**). After metatarsal shortening osteotomies were performed (**c**), the callosities were spontaneously relieved in the long term (**d**)

ses in the future after the development of the gonarthrosis [11].

The alignment and rotation of the lower extremity have been developed in harmony with surrounding ligaments and muscles. Patella joins this harmony positioned in/and between a tendon and ligament. It transfers load from the hip to the tibia and stabilizes the joint in many ways. *Q* angle is the angle between the quadriceps muscle and the patellar tendon and determines the direction of the forces affecting the patella. Any change in pelvic angle, hip anteversion, tibiofemoral angle, tibial torsion, navicular drop, the existence of genu recurvatum, and femoral and tibial length also affects the *Q* angle and may alter the direction of the forces and load distribution at patellofemoral joint [12]. This situation is the main reason for patellofemoral osteoarthritis and knee pain. There are several prophylactic surgical procedures, including soft tissue interventions, bony interventions, and combined to prevent this condition. For example, Maquet osteotomy, Elmslie-Trillat osteotomy, and Fulkerson osteotomy are the procedures mostly used to restore the Q angle by distal realignment of the patellar tendon [13–15]. Medial patellofemoral ligament (MPFL) reconstruction, lateral retinacular release, and medial plication are some examples of soft tissue interventions [16]. Depending on the extent of the pathology, these procedures with derotational osteotomies of the femur and/or tibia may also be used to restore the anatomy [17] (Fig. 35.4).

There is a unique longitudinal alignment between the femur and tibia, both on sagittal and coronal planes. Disruptions, particularly on the coronal plane, lead to genu varum (the main reason for medial knee pain and osteoarthritis) or genu valgum [18]. In pediatric age, trauma, infection, radiation, or some metabolic diseases may cause physeal arrest of the proximal tibia or distal femur. These conditions may lead to imbalanced longitudinal growth and deformity in three planes around the knee. To prevent the development of malalignment in any plane, physeal bar excision, epiphysiodesis, and limb lengthening or deformity correction with circular fixation, or a combination of these techniques can be used [19] (Fig. 35.5). However, treatment strategies for adults are different for coronal knee deformities. These patholo-

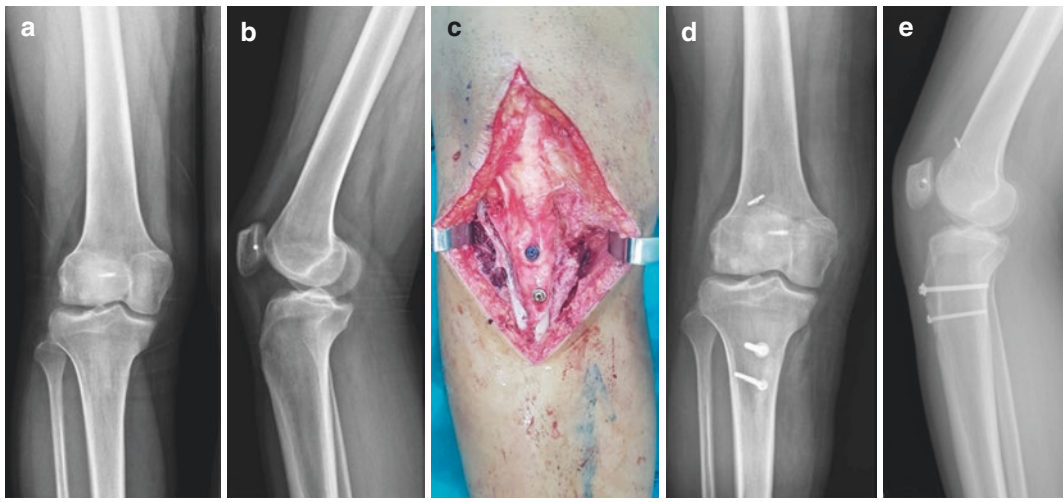

Fig. 35.4 (**a**, **b**) Preoperative X-rays of a 23-year-old patient with patellar instability. The patient had undergone an unsuccessful MPFL repair surgery 3 years ago and now complaining from anterior knee pain and feeling of subluxation. (**c**) Intraoperative image showing the medial transfer of the patellar tendon. (**d**, **e**) Postoperative AP and lateral X-rays showing patellofemoral ligament reconstruction using hamstring allograft and distal patellar tendon realignment using Elmslie-Trillat osteotomy technique. Note the centered patella on the femur when compared to preoperative X-rays

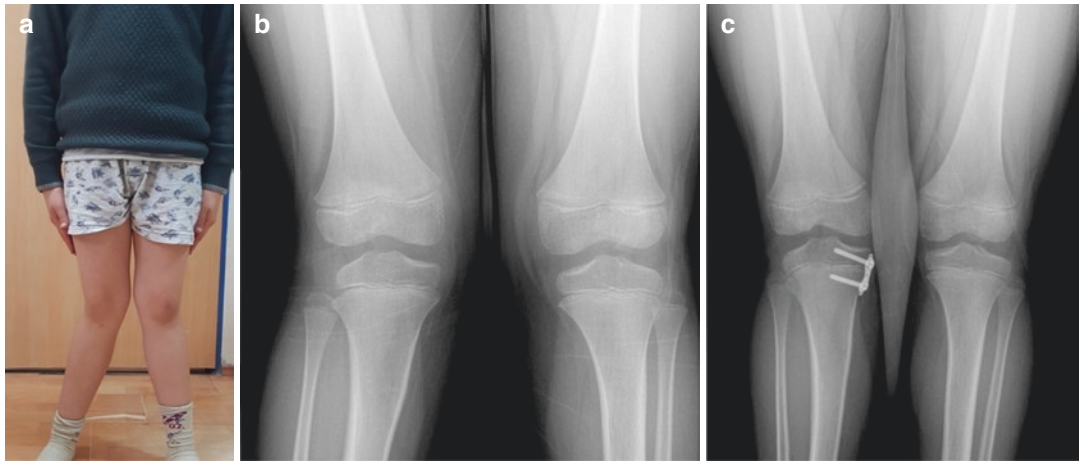

Fig. 35.5 (**a**) A 6-year-old boy sustained a lateral tibial physeal arrest after conservatively treated proximal tibia fracture. After 3 years of follow-up, the patient developed a genu valgum deformity namely "Cozen deformity" on the right side. (**b**) AP preoperative X-rays of both knees showing lateral growth arrest and progressive genu valgum. A medial epiphysiodesis with a plate was carried out for the patient. (**c**) Postoperative AP X-rays after 7 months showing remarkable improvement in alignment

gies can be addressed using proximal tibial osteotomies [20]. Genu valgum is a relatively rare pathology, and most of the surgeons have defined procedures focusing on correcting the genu varum. Proximal tibial lateral closed or medial open osteotomies have been reported to be very effective to restore the alignment, prevent the development of the osteoarthritis, and alleviate the medial knee pain. However, all these procedures have potential complications like deep vein thrombosis, peroneal nerve palsy, wound infections, nonunion, etc. From this point of view, surgeons have currently focused on a different concept to prevent knee pain and osteoarthritis [21].

The theory "asymmetrical subsidence" claims that the proximal tibial plateau has a relatively soft metaphysis prone to osteoporosis by the age. As the lateral tibia plateau is supported by three cortexes (two fibular and one lateral tibial cortex) and medial plateau by one cortex, a subsiding much more severe on the medial side may occur and lead to the development of a genu varum and medial knee compartment osteoarthritis [21]. From this point of view, resection of the fibula with or without arthroscopic debridement of the knee and/or medial high tibial osteotomy for selective cases has been reported to be a safe, promising, and more biological way as a prophylactic surgical procedure (Fig. 35.6).This procedure must be performed for patients with a varus less than 5°, as the patients with severe varus have been reported not to benefit from only fibular resection [11].

35.5 Prophylactic Surgery to Prevent Hip Osteoarthritis Due to Acetabular Dysplasia

The hip joint connects the lower limb to the trunk and provides a basis for the upright posture and balanced movement. The hip joint is supported by a large number of ligaments and surrounding muscles during hip movements, thereby producing unlimited movement modifications and amplifications [22]. The hip joint is a ball-and-socket-type joint. Socket part is formed by *os pubis*, *os ischii*, and *os ilii* connected with Y-shaped triradiate cartilage. And the ball part is the head of the femur. In acetabular dysplasia, a developmental deficiency exists on the acetabular side of this joint. The acetabulum continues to develop up until the ages of 8–13, and any kind of interruption of the growth eventually leads to an acetabulum deficiency [23]. This interruption of the growth may occur due to the

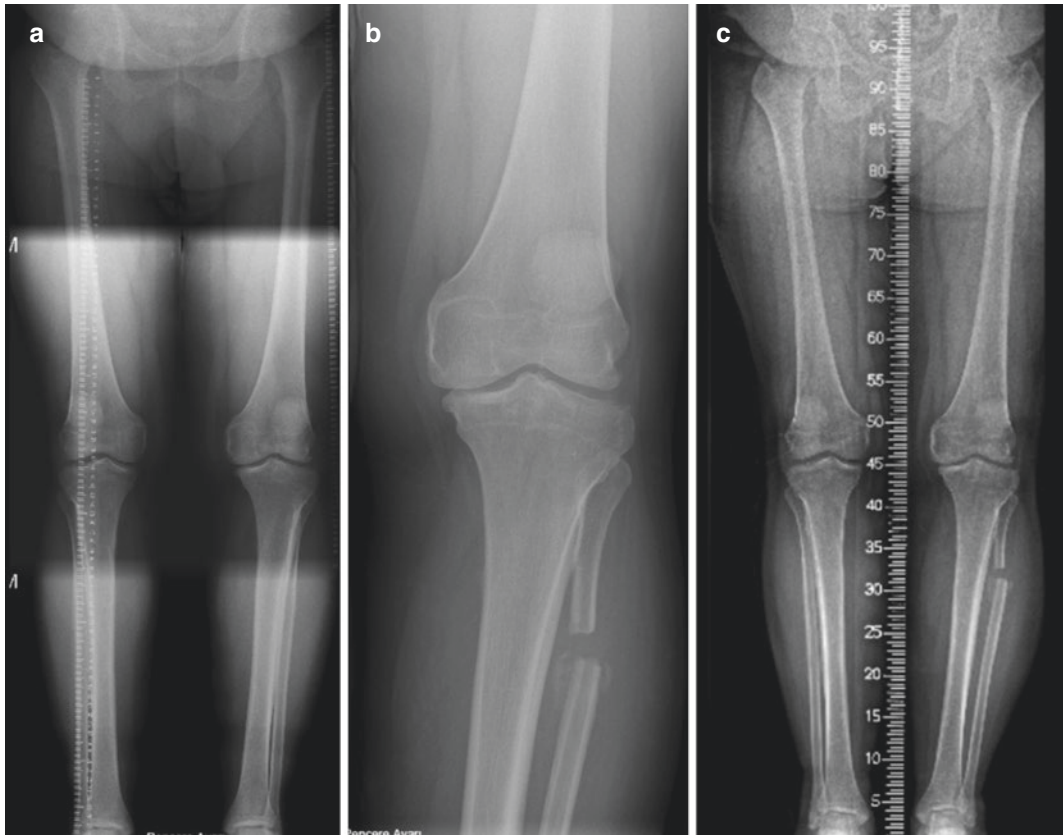

Fig. 35.6 (**a**) Preoperative orthoroentgenogram of a 40-year-old man complaining left knee medial compartment pain. The X-ray revealed an onset of osteoarthritis in the medial compartment and 3° varus malalignment. (**b**) AP postoperative X-ray showing segmental fibular resection performed. Also, arthroscopic debridement of the joint was carried out. (**c**) Postoperative orthoroentgenogram in the third month. Although there was no radiological improvement in the alignment, the patient returned to daily activities with a pain-free knee joint

injury or infection of the triradiate cartilage or the inadequate treatment of a previous developmental dysplasia of the hip (DDH), etc. [24]. In most cases, there is a deficiency in the anterolateral wall of the acetabulum. However, the deficiency can be detected in the posterior wall as well. Although it varies according to the amount, shape, and place of the dysplasia, dislocation, subluxation, or secondary osteoarthritis almost always occur later in life due to imbalanced and inharmonious movements between the femur and acetabulum. Depending on the amount of dysplasia, degenerative complaints frequently arise in adolescents. However, the onset of the symptoms may not be seen until the sixth decade of life as well [25]. Since hip dysplasia is a pathology with the risk of creating irreversible problems in the patient's future life, it should be treated prophylactically with various methods to prevent degenerative changes even if it does not cause complaints as soon as it is noticed until the fifth decade of life [26].

35.6 Prophylactic Interventions for Acetabular Dysplasia from Infancy to the Age of 8 Years

In the early examination in infants, positive Barlow and Ortolani tests are indicative of unstable hip dislocation. Although there are several reasons for this condition, the most common factor is the loose capsule, which can-

not keep the femoral head in the acetabulum. The first prophylactic treatment of acetabular dysplasia begins at this stage, and this is when the treatment is easy and most effective. Because keeping the femoral head in acetabulum by preventing the dislocation of the head or with the reduction of a dislocated head applies pressure to the triradiate cartilage, and acetabulum starts to reshape and develop. This often results in a gradual deepening and decrease in the inclination of the acetabulum. However, this is not always the case, and the acetabulum can remain shallow and inclined (acetabular dysplasia) more than normal ranges. Hip ultrasonography is now being routinely performed for newborns, usually 6 weeks after birth for the DDH survey. Graf type 2b, c, and d hips are dysplastic hips and need to be treated prophylactically to prevent further deterioration of the hip joint [27]. Using a Pavlik harness for 6 weeks is the most preferred way of the treatment [28]. The aim is still the same; directing the femoral head to the acetabulum with the harness and keeping it in the acetabulum. Although there are several different opinions, closed reduction with or without adductor tenotomy and preservation of the reduction in a hip spica cast (pelvipedal) for 3 months is the most preferred treatment choice for children between the 6 and 12 months old with persistent or newly diagnosed dysplasia. If a closed reduction cannot be achieved, an open reduction using a medial approach is performed at this stage [29]. The closed reduction generally may not be effective to reduce the hip after 12 months. Thus, an open reduction using a medial, anterior, or anteromedial incision is used to intervene in the soft tissues that hinder the concentric reduction of the hip. The preferred approach is the anterior incision. After the procedure, the reduction must be preserved in a hip spica cast for 3 months. For dysplasia that persists after 18 months, both bone and soft tissue interventions are required. The goal is to increase the anterolateral acetabular coverage, and the need for additional procedures like capsulorrhaphy and other interventions are performed according to the severity of the case [30]. Although many different types of osteotomies have been defined, Salter and Dega osteotomy is the most performed osteotomy in this stage (Fig. 35.7). However, Pemberton, Pembersal, and many other osteotomy techniques can also be used for this age group. All these techniques have special indications and are used for particular cases until the age of 8. Even though there are controversies about the age limit, it is assumed that simple iliac osteotomies may not be sufficient to provide coverage due to the closed triradiate cartilage after 8 years of age. Thus, after the closure of the triradiate cartilage in any age, osteotomization of three pelvic bones (ilium, ischium, and pubis) is needed for the redirection of the acetabulum.

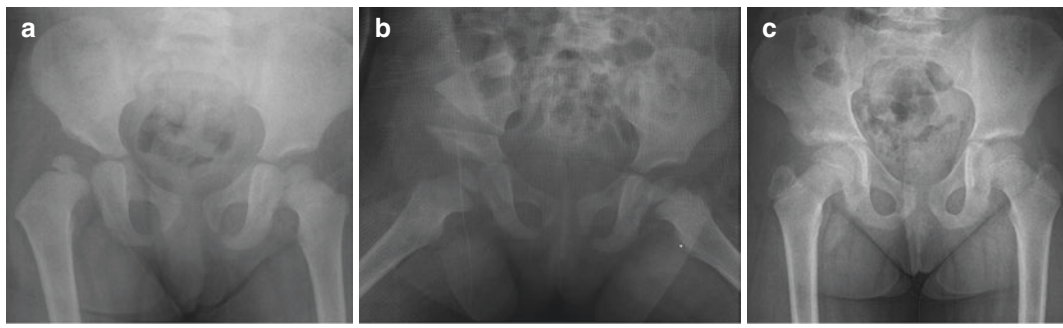

Fig. 35.7 (**a**) AP X-ray of a 22-month-old girl showing the incidentally diagnosed dysplasia of the right hip. (**b**) Initial postoperative AP X-ray showing perfect anterolateral coverage of the hip after a modified Salter osteotomy procedure**.** (**c**) AP X-ray at postoperative seventh year showing perfect development of the acetabulum without any residual dysplasia

35.7 Prophylactic Surgery for Acetabular Dysplasia in Adolescents and Adults

In untreated or incidentally diagnosed cases, the femoral head forms an unstable joint surface that constantly goes up and down with the edge of the acetabulum (Fig. 35.6a). This instability often creates degenerative changes that occur in young adolescents and generally progresses within a few years. If the acetabulum is redirected, the forces on the femur head will be distributed on a larger surface, and this can prevent and even reverse degenerative changes [31]. This is why a groin pain increasing with flexion and internal rotation of the hip must be a warning sign of dysplasia in adolescents and young adults. Although 8 years of age is debatable, according to the general opinion, the triradiate cartilage closes and does not function after this age. Redirecting or reshaping the acetabulum with the aforementioned techniques becomes impossible, as closed triradiate cartilage does not bend with simple osteotomies like Salter osteotomy [23]. Thus, more complicated osteotomies must be employed after this age group. If the triradiate cartilage is still open between the ages 8 and 15, triple innominate osteotomy (Steel, Tönis), double innominate osteotomyi (Sutherland), or Dega osteotomy can be performed to remediate the defective coverage of the acetabulum. However, if the patient is older than 15, more complicated procedures like incomplete triple pelvic osteotomy (a modified form of Steel osteotomy, ITPO) (Fig. 35.8), triple innominate osteotomy (Steel), Ganz (Bern) [32], or spherical osteotomies (Wagner, Epright) are inevitable. The choice of the technique depends on the surgeon's experience and concentric reduction of the hip detected with preoperative abduction-internal rotation AP X-ray of the affected hip joint. ITPO is a good and applicable technique in cases with a concentric reduction [33]. Although Steel osteotomy is preferable for slight and moderate dysplasias, Ganz osteotomy could be better in severe cases. Cases in which concentric reduction cannot be achieved, salvage procedures like Chiari osteotomy and shelf acetabuloplasty can be performed. These techniques do not prevent degenerative changes, however, they prevent subluxation and dislocation of the hip.

35.8 Conclusion

Timely implementation of prophylactic surgery in orthopedics is usually associated with decreased patient morbidity. Prophylactic surgery obviates the need of more extensive surgical procedures with more complications by decreas-

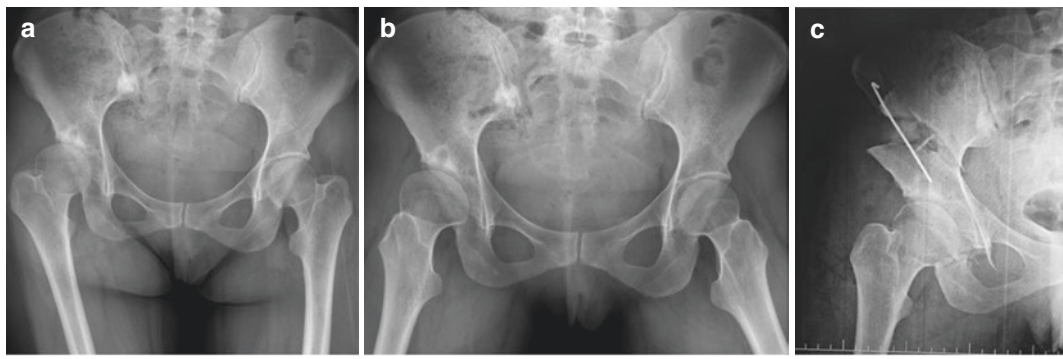

Fig. 35.8 (**a**) AP X-ray of a 34-year-old woman showing dysplasia of the right hip. Subchondral cyst at the acetabulum is an indicator of the onset of degeneration and osteoarthritis. (**b**) Abduction-internal rotation AP X-ray showing concentric reduction of the hip, which means that a prophylactic redirectional osteotomy may be beneficial for this patient. (**c**) Initial postoperative AP X-ray of the right hip showing perfect anterolateral coverage of the hip after an incomplete triple pelvic osteotomy without lateralization or retroversion of the acetabulum

ing or sometimes eliminating the disease progression and also becoming popular as a part of the rediscovering the importance of public healthcare in recent years.

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36 Ethical and Legal Dimensions of Prophylactic Surgery

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36.1 Introduction

Cancer is responsible for the death of one in every six people worldwide [1]. In the distribution of cancer within itself, it is estimated that 3–20% of the cases are assumed to be linked to some genetically inherited genes [2]. These genes not only increase the risk of cancer, but also have severe and fatal consequences. While breast or ovarian cancer incidence in normal individuals, one of the most well-known types of genetic cancer, varies between 1 and 12%, this probability can reach up to 85–86% in people carrying *BRCA1* and *BRCA2* genes. Therefore, identifying the genes that inherently carry a potential cancer risk can allow new opportunities to detect, prevent, and treat many diseases. Thanks to the rapidly emerging developments in biology and medicine and the Human Genome Project, genetic tests have started to be used as a novel means of preventing diseases with their ability to early diagnose a potential disease. Genetic testing refers to the medical examinations that aim to reveal or detect the presence of a person's hereditary diseases or predisposition to these diseases either directly or indirectly by examining genetic inheritance conditions [3, 4]. According to the result of the test, an individual with a genetic predisposition to a given disease is provided with the opportunity to plan for the future and with the chance to prevent the adverse effects of the disease.

Until recently, patients with a genetic predisposition to cancer were recommended follow up for early clinical diagnosis and treatment, and in some cases, the case ended up with chemotherapy. However, these approaches being inapplicable or ineffective in some types of cancer have paved the road for the prophylactic surgical method, one of the most important risk reduction initiatives. In fact, prophylactic surgery is not a recent one. However, it has been one of the frequently debated and implemented methods in treating certain diseases [5]. The main factor that leads this method to be frequently debated today is that it poses some legal and ethical problems despite its great success in reducing risk. Before addressing these problems, it is necessary to consider what this method is briefly. Prophylactic surgery, also known as preventive surgery, is a method that enables the risk to be significantly reduced or eliminated as a result of completely or partially removing the organ on which cancer may develop. After applying this method, mortality rates can be decreased by 89.5–100% [6–8].

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With this method, it is aimed to prolong the mean-life expectancy. However, the efficiency of this method on the quality of life varies from individual to individual, which may be caused by due to the genetic inheritance pattern problem of the disease, in which the problem cannot be sorted out by just removing organs. Some concomitant conditions may continue to be observed in different ways in other organs and also due to the psychological reasons and physical changes observed post-surgery [6]. In this context, such examples from a wide variety of spectrum as the emergence of drug addictions, restrictions on social and working life, the emergence of personal disabilities or deficiencies, early menopause, depression, decreased sexual desire, change of body perception, inability to have child, and changes in family dynamics can also be observed [6]. Especially concerning *BRCA* genes, breast removal (mastectomy) causes a serious change in body perception, and breast implant surgery is frequently resorted to following prophylactic surgery [9]. The most important setback of the intervention is that it is irreversible. Therefore, it is thought that the operation should only be applied when the benefits outweigh the risks [9]. However, the benefits and risks that can arise from this intervention are partially unknown. Even if the risk of mortality and recurrence of cancer decrease following the surgical intervention in question, there are serious social and psychological effects of such a large surgical intervention. Such a difficult decision that needs to be made considering the social and psychological effects requires an ethical approach, thus requiring a review from a legal aspect. During this investigation, it is necessary to look at the issue from the perspective of human rights. Surgical intervention with a biomedical origin is directly related to such fundamental rights, as the right to life and confidentiality raises the legal obligation to protect human rights and human dignity. In this context, we will first underscore the timeline, starting from the detection of genetic risk to the operation and the accompanying problems that may arise at this stage. Later, the application of the prophylactic method and the post-intervention phase will be examined legally. The reason why we examine making such staging is that the ethical and legal problems in question are mostly concentrated in these two stages.

36.2 Detection of Genetic Risk

Various legal and ethical problems may arise in the stages, starting from genetic risk detection to resort to the risk-reducing intervention. Since the prophylactic intervention is a treatment applied with the aim of providing medical relief, it gives rise to a special relationship between the patient and the doctor, together with some responsibilities specific to the nature of this emerging relationship. Respecting confidentiality and the obligation of illumination is of particular importance for these issues. Attributing a special meaning to these obligations results mainly from the nature of the genetic information on which the intervention is based, not from the intervention procedures. Namely, the information obtained from gene analysis belongs to the person's identity and, therefore, must be protected [10]. However, using such information in an unfair and harmful manner may give rise to more comprehensive consequences than the ordinary health data itself. The European Court of Human Rights concluded that DNA profiles contain a large amount of personal data [11]. Therefore, it is possible to use genetic information, which includes comprehensive information about a person's belonging to a certain group and his/her health status in parallel with discriminative purposes. Indeed, the Nazis can be given as a historical and real example of the abuse of genetic information for the purpose of racism and genocide. Therefore, the concept of "genetic exceptionalism" is used by some authors to express that genetic information is different from other data related to health [12, 13]. According to those who advocate this view, genetic information is unique since it provides information about the person's current and prospective health status and the health status of the family members, and even about the next gen-

erations [13–19]. An opposing view of which approaches with suspicion toward this view states that it is not possible theoretically and practically to separate genetic information and health information from each other [20].

Such an assessment related to genetic information also bears noteworthy legal consequences. If we accept that there is no difference between genetic information and data related to health in terms of qualification, international regulations regarding the protection of health information and data such as the European Charter of Patients' Rights, the Amsterdam and Lisbon Declaration, may be considered sufficient for the protection of genetic information. However, in the event that a possible difference is considered, genetic information will need to be specially protected. Although there is no consensus on this matter, some international conventions dwell on this subject. The first of these is the Convention for the Protection of Human Rights and Human Dignity concerning Biology and Medicine, and the first binding international contract in its field adopted in 1997: Convention on Human Rights and Biomedicine Agreement. It is clearly stated in Article 11 of the related convention that no discrimination can be applied to anyone due to their genetic inheritance. Another legal text that directly prohibits genetic discrimination is the Universal Declaration on the Human Genome and Human Rights, released by UNESCO. In Article 6 of this declaration, nobody can be discriminated against due to their genetic structure; otherwise, in this case, some consequences that may harm human rights, fundamental freedoms, and human dignity can occur.

Nevertheless, the reflection of discrimination due to individuals' hereditary characteristics on existing human rights texts came to the agenda later concerning the developments in genetics [17]. For this reason, genetics is not explicitly included as a reason for discrimination in such essential human rights texts as the Universal Declaration of Human Rights and the European Convention on Human Rights (ECHR). However, since the causes of discrimination are not conclusive in international conventions, they also cover genetic discrimination. As can be seen, genetic discrimination has been considered as an issue that needs to be regulated in documents dealing with human rights. In this regard, this issue is regarded as a human rights issue in the international arena.

36.2.1 Protection of Genetic Information: Confidentiality

Genetic discrimination is defined as discrimination observed against the individual or the individual's family members due to real or perceived differences other than the "normal" genotype [21]. The most frequently expressed fear in individuals with genetic risk is the use of genetic information in a way that may end up with discrimination [22]. Indeed, one of the areas where abuse of genetic information has the most comprehensive consequences is the issue of discrimination. Due to hereditary characteristics, individuals may not benefit from equal conditions in decision-making processes in different fields, such as health and life insurances, employment, custody, adoption, admission to a school, or loan application [21]. Therefore, failure to protect information related to genetic diseases and violation of confidentiality may leave the individual as a victim in many life areas. The issue of genetic discrimination, which has come to the fore, especially in employment[1] and insurance law, has prompted some states to make special arrangements regarding the issue [23]. In the USA, for example, the regulations envisioned by states in the 1970s on a federal basis were followed by such regulations as the Americans' Disabled Americans Act (ADA) and American Health Insurance and Portability and Responsibility Act (HIPAA) [24, 25]. However,

[1]The main reason for discrimination in the employment field is that employers want to work with healthy people, believing that productivity will decrease and increase costs. On the other hand, insurance companies use information about the health status of the insurant or the person who wishes to be insured to protect and increase their profitability.

the Genetic Information Nondiscrimination Act was adopted in 2008 since these regulations were far from providing sufficient assurance.[2] With this law, discrimination based on genetic information was prohibited in health insurance and working areas. It is possible to see similar regulations in some countries, such as Canada, England, Austria, Germany, and Switzerland. For instance, with the Genetic Diagnostics Act of 2009 in Germany, the subject was specially regulated. It was legally set forth that insurers shall not demand genetic testing and also no information about previous genetic tests[3] of the individuals [26]. In Switzerland, The Bill regarding Genetic İnvestigations in Humans, rules that insurance companies shall not request genetic reviews or use previous test results. However, it remains doubtful how successful these regulations are in protecting people's confidentiality with genetic risk and preventing discrimination because genetic tests are not the only source of information about individuals' susceptibility to a certain disease or risk. Indeed, some of the first documented cases of genetic discrimination in America include implications from the individuals' particular family history [27]. However, we previously stated that genetic testing includes information about individuals and family members of the individuals as well. Some of the arrangements mentioned above provide only protection for the insurant and remain silent about using the insurant's test result arrangements. Even if employers and insurance companies are prohibited from accessing genetic test results, they may have some justified interests in accessing individuals' health data. In this case, how health data and genetic information can be separated is another problem that needs to be resolved. Therefore, it seems possible for employers and insurance companies to learn and use various information sources about genetic risk despite these regulations. For this reason, such various segments as physicians and genetic counselors with direct access to genetic information should act more carefully than other health data of the individuals in terms of keeping this information confidential. Otherwise, possible criminal and legal consequences may arise since the patient's confidentiality is severely breached.

Another issue that needs to be discussed in terms of confidentiality concerns the sharing of genetic information with family members. Undoubtedly, family members are most likely to be affected by the individual's test results at risk. For this reason, it is thought that information about the test results should be shared with family members. If the patient shares this information with his/her family or consents it to be shared, no legal problem can be mentioned. However, some patients may not consent to share their information with various concerns like family dynamics, geographical and social distance, and the test results being not related to family members [28]. In this case, such things as how to act and how to solve the legal and ethical problems may remain controversial. The focus of this discourse is how to balance the patient's confidentiality with the overall interest of family members. As is known, due to the trust relationship established between the patient and the doctor, the confidentiality of the patient should be respected. In this context, the medical evaluations about the patient should be confidentially conducted, and unless the nature of the disease requires, the personal and family life of the patient should not be interfered with [29].

Despite the person's given consent, sharing the genetic information with the family may lead to violations of confidentiality and, together with some consequences, within an unknown scope. It is also possible to inform the other family members about the genetic risk to let them take precautions against the possible disease, which

[2]The use of genetic information is not clearly regulated in the law in question. However, to investigate in terms of discrimination, those who have genetic risk should be evaluated as "disabled" under the law. Although the Equal Employment Opportunity Commission (EEOC), which determines the principles of implementation of the contract, was included under the title of disability, the subject gave rise to various American doctrine debates.

[3]In Article 18 of the mentioned law, an exception is stipulated for this rule regarding the high amount of insurance contracts. Accordingly, test results can be taken into account for life insurances exceeding 300,000 euros.

may require disclosure of special information [16]. For this reason, many scholars believe that the moral obligation to inform family members about genetic risks lies upon the doctor's side [4]. However, it is not clear how to balance the confidentiality of the individual at risk and the sharing of any information related to the individual. We believe that the balance that needs to be established between the confidentiality of the individual at risk and the sharing of information should be established following the conditions of the concrete events, especially considering the person's family dynamics. For this reason, it does not seem possible to give a precise answer to this question covering all instances. Failure to give an exact answer to this question gives rise to an uncertain situation for physicians. It paves the way for legal and ethical problems. Therefore, it is imperative to regulate this issue with legal regulations. Regarding the issue, if various states' legislation is examined, the general trend is to protect confidentiality [30]. The main difference among countries is observed in terms of the scope of this protection. For example, France and Sweden seek absolute consent and authority for family members' access to genetic information [31]. On the other hand, in countries such as America, Austria, Japan, Singapore, Israel, England, Canada, sharing genetic information under certain conditions is deemed possible, even if there is no individual consent. We see that the difference lies in these exceptional cases. Generally, the case of preventing death, illness, or severe injury of family members has been regulated as an exception. It is stated in Singapore that the physician may have a legal responsibility to warn family members in the event of a serious genetic risk [32]. While Austria seeks "serious" conditions, the USA and Canada refer to "exceptional and compelling" conditions, and Israel refers to "severe" conditions in such cases [33]. Unlike other regulations, it is considered sufficient to share New Zealand information when it is relevant to family members [34]. It should be noted that the regulations made in the international arenas on the subject are in the same direction. The Committee of the Council of Europe adopted the principle of not disclosing personal information in principle 9 of recommendation numbered R (92) 3 on 10.02.1992. However, it was stated that this rule could be exempted if there are severe genetic risks for other family members. As can be seen, while many legal regulations have adopted confidentiality as an important rule, they brought an exception to this rule in cases where serious and severe consequences could occur for family members' interest. Therefore, the general tendency is to protect neither absolute confidentiality nor third parties. In terms of the concrete event, the individual or the committee (which may be a physician or ethics committee) will try to set between these two values. In our opinion, conducting such an investigation based on a concrete event will ensure that the conditions in which the individual undergoing genetic testing will also be taken into account [35].

36.2.2 Illumination and Consent

After determining the genetic risk, another issue that may raise legal and ethical problems is the obligation of illumination. The patient's rights over his/her body require that the person should be the determining party during a medical intervention. Therefore, consent is sought as a prerequisite to say that medical interventions are lawful. In such interventions, the necessity of seeking consent as a source of lawfulness is considered necessary not only in terms of law, but also in the ethical evaluation of the issue. However, for the consent given for the intervention to be valid, the patient must be thoroughly and detailedly illuminated. The obligation of illumination can be briefly defined as a necessity to provide the required information to the individual who will undergo the physician's procedure before any medical intervention is planned. In this context, if the patient does not accept the recommendation, the physician must convey the consequences of various treatment modalities and their benefits as well as the risks and possible complications. It should also be mentioned that the test result

indicates an existing risk rather than an existing disease, especially in cases of genetic diagnosis because some patients may tend to consider the results of genetic testing as an irreversible indication, which may affect the decision-making phase. Therefore, in interventions based on genetic testing, physicians should be more sensitive about the patient's illumination and should obtain the patient's consent within this framework. However, prophylactic surgery is a frequently used method, especially for genetically transmitted diseases, but it is also a method that can be brought to the agenda with the increasing risk in many diseases that do not exhibit hereditary transition cause cancer. For example, the gallstones of a patient who has no complaint related to gallbladder can be removed from gallstones during surgery. However, in order for this intervention to be accepted as lawful, physicians must obtain the patient's consent by illuminating the patient before the intervention from a perspective that there are stones in the gall and that this may cause serious problems in the future. Otherwise, the prevention and elimination of a risk detected during the operation without the patient's consent may end with some outcomes for the physician's side.

Another point to consider when it comes to risk reduction methods is the probability that this method may not eliminate potential risk and that the presence of risk may prevail, though in a decreasing trend. This is more important in prophylactic surgery, which has severe social, psychological, and physical results. As mentioned earlier, the method mentioned above requires removing a potential risk but at the same time healthy organ, which can lead to irreversible and irrecoverable consequences. Those with a large intestine may have to wear a lifetime colostomy bag, and patients who receive a pancreas may have to use insulin medicine for a lifetime, women may lose their reproductive ability, and children who have their thyroid removed may be forced to use drugs for life. For this reason, physicians should convey the results of alternative treatments and irrecoverable results to the patients, considering their age and marital status. However, the physician must express his/her thoughts on the application of the prophylactic method to the patient explicitly because the researches show that the decision-making process for the prophylactic method is especially difficult for women and open to be affected due to the familial nature of the genetic test [36]. After Angelina Jolie underwent a bilateral prophylactic mastectomy, this surgical procedure's demand has increased significantly among women [8]. This situation reveals that although a positive development occurs for women with genetic risk, the individual may not always make an objective decision during the decision-making process. Therefore, physicians should clearly demonstrate the potential risks and the benefits to be obtained at the end of the operation. However, it may not always be possible to reveal the benefits and risks in the prophylactic method, as it is implemented not to improve the current health condition, but to protect against prospective diseases [37]. Consequently, due to this method's nature, the scope of the obligation of illumination expands. It leaves the responsibility to the physician's side in terms of giving detailed information about the purpose and application of the intervention in addition to the risks and benefits. However, the patient, who does not want the application of this method for various reasons, should also be informed about the disadvantages and alternative methods that can be followed. Otherwise, it can be speculated that the physician has not fully fulfilled the obligation of illumination. A doctor who recommended a test that should be performed concerning the diagnosis of cancer in a case in America, who at the same time did not illuminate the patient about the drawbacks of refusing to take the test, was found faulty as the patient died of cancer [38]. The decision in question is the first decision that imposes responsibility on a physician for an act of neglect without any physical intervention [39]. Of course, the physician cannot inform about the intervention process and afterward, with all of the risks and benefits. For this reason, the point that is important in terms of the obligation of illumination should be to bring the

patient to a position, where he/she gives the decision about his/her future with his/her own will, considering the risks and the benefits he/she can get. For this, it should be stated that the physician has the duty of providing consultation about all material risks that a reasonable person would like to be informed about before making a decision [39].

36.3 Implementation of Prophylactic Method and Post-intervention

The main issue to be considered regarding the prophylactic method, which aims a risk reduction, is in compliance with the subject in question with the concept of lawfulness. As is known, interventions other than medical necessities can damage a person's body integrity. For this reason, only the medical interventions considered compulsory according to medical science, namely those based on indication, are considered lawful. Therefore, there should be a legal or medical ground that justifies why the physician initiates the diagnosis and treatment process. However, with its primary aim of preventing disease rather than healing it, the prophylactic method comes to the fore. It gives rise to debates in terms of lawfulness because the application of such an intervention with the potential to create serious physical, psychological, and social problems based merely on the patient's consent with no indication can put the physician under criminal and legal responsibility.

The point that medical science has reached today causes the indication to be discussed and interpreted again. The obligation of indication, which was previously regarded as one of the basic elements of medical intervention, has expanded as a concept with modern medicine development. Therefore, a reconsideration of social and psychological causes within the indication concept has started [40]. It has been even argued that the patient's consent could replace the indication [29]. According to this view advocated in the German doctrine, consent, in the absence of an indication, allows the intervention to be legitimate, only when it fits within morality and manners, not harming the addressee and complying with the duty of care [41]. According to the opinion mentioned earlier, consent and indication are not cumulative but alternative criteria of medical intervention. In our opinion, it does not seem possible to agree with this view. The rule of law has not vested the people with the right to dispose of their lives and bodily integrity as they wish. The law also undertakes the duty to protect people event against their own will. Therefore, the consent of the victim only makes the medical intervention legitimate when the indication is present. For this reason, it is necessary to make special legal regulations for such controversial situations as organ and tissue transplantation, esthetic operations with no indication in terms of legality, and legitimacy of the intervention [42]. In the study in question, consent and indication were accepted as cumulative conditions that make medical intervention legitimate and evaluated accordingly.

Since the discussion on the concept of indication exceeds this study's scope, it should be contented with giving brief information on the subject. Although the prophylactic method does not aim to treat an existing disease or to prevent a potential danger to be caused by it, it is intended to eliminate the potential risk that a person may encounter as a result of a genetic anomaly. In this regard, the reason for the application of the said method is the protection of the individual at risk. Therefore, given the meaning of the concept of indication today, it should be accepted that the concept covers not only the measures to eliminate the disease, but also diagnostic and preventive interventions along with it. Interventions that are mandatory for diagnosis, treatment, and protection are accepted as indications in the doctrine. In this respect, it should be accepted that the prophylactic method, which serves to reduce the risk and thus protects the patient from the disease which has the potential to develop in the late stages, also provides the indication requirement. Besides, due to the positive effects of the method in question on psy-

chology, it is also possible to evaluate it within a psychological indication.[4] However, at this point, it should be stated that the social or psychological indication should be based on concrete data. In a good example of a decision on the related matter, New York Supreme Court ruled that a psychological condition that might give rise to a medical necessity was not enough to justify the procedure of a bilateral mastectomy surgery aimed at eliminating gynecomastia symptoms. Although the 17-year-old had experienced emotional distress and depression due to symptoms, the court ruled that no psychiatrist, psychologist, or medical specialist, including the pediatrician, had been consulted, thus ruling that the feeling of embarrassment was not sufficient alone for medical necessity [43, 44].

Considering the legal regulations and decisions regarding the concept of indication, we can say that the aim of protection and prevention is also included. An exemplary regulation in this regard can be given from Turkish law. The purpose of diagnosis, treatment, and protection is considered a medical requirement in the third paragraph of the 13th Article of the Medical Deontology Regulation and the 12th Article of the Patient Rights Regulation. Another example can be given in American law. In the California Welfare and Institutions Code 14059.5, the concept of medical necessity is defined as follows: "A service is medically necessary or a medical necessity when it is reasonable and necessary to protect life, to prevent significant illness or significant disability, or to alleviate severe pain." Florida District Court of Appeals defined the concept of medical necessity in Gallagher Bassett Services, Orlando v. Mathis decision as: "Medically necessary" or "medical necessity" means any medical service or medical supply, which is used to identify or treat an illness or injury, is appropriate to the patient's diagnosis and status of recovery and is consistent with the location of service, the level of care provided, and applicable practice parameters. The service should be widely accepted among practicing healthcare providers, based on scientific criteria, and determined to be reasonably safe. The service must not be of an experimental, investigative, or research nature [45]. Although the aim of protection is not mentioned in the decision in question, it is claimed in the related doctrine that preventive medical interventions have "an indirect aim of treatment" [40, 41, 46]. Therefore, the concept of treatment can be defined as the whole of measures taken, medications, or surgical interventions to reduce the risk of a disease, as well as to eliminate and cure a disease [47]. In this respect, discussions on prophylactic interventions depend on the meaning to be attributed to the concept of treatment. At this point, it is necessary to state that there are court decisions that consider individuals' carrying genetic risk as a disease [48]. Suppose the approach followed in the court decisions in question is adopted. In that case, the indication will not need to be separately discussed since the prophylactic method can be started to be considered therapeutic because there is an existing disease. However, since there is no consensus neither in America nor internationally, it is necessary to evaluate whether the obligation of indication exists before applying each prophylactic method. The physician cannot apply such a surgical method to remove a healthy organ as prophylactic surgery without concrete data revealing the indication. Otherwise, the intervention will not be considered lawful, and the physician will be held deliberately responsible for his/her actions.

In addition to the interventions caused by genetic risk, sailors who are about to sail away or go mountain climbing to a country with poor health services sometimes resort to prophylactic appendectomy as a preventive measure in their expeditions exploring space or the north pole [37]. In this case, since there is no genetic factor that tends to develop into a disease, it is seen that the obligation of indication remains uncertain. For this reason, it is suggested that prophylactic

[4]According to Gürelli, it can be accepted legitimate to correct a disorder of the organ from which this disorder originates to correct mental disorders stemming from organic origin. At the same time, surgery and interventions aimed at changing the symptoms with psychiatric indications should be considered unlawful.

surgery can be performed if the complication rates resulting from prophylactic appendectomy are low enough, and the incidence of appendicitis is sufficiently high [49]. Before a prophylactic intervention that does not originate from genetic risk, more reasonable remedies should be sought other than removing a healthy organ. In the absence of such an alternative, intervention should not be performed without carefully evaluating potential complications [49, 50]. However, since such an intervention can be foreseen as a prerequisite for starting a job, it also requires evaluating whether the free will of the person is under pressure. In addition to the obligation of indication, it must be performed with the care and attention required by medical science and its application for a medical intervention to be considered lawful. Medical care and attention are also sought in the prophylactic method. In this context, the physician should carry out the operation and treatment required by the medical science, avoid unprotected interventions, take appropriate measures for the complications that could occur, following the infection and hygiene rules, and the patient's condition required. However, such interventions' success is linked with the removal of tissue with the risk of developing cancer, so the extent and the way physician removes the tissue gives another subject to us to be evaluated separately in terms of care and attention. Apart from this, there is no significant difference between the usual medical interventions and the prophylactic method.

36.4 Conclusions

Nowadays, prophylactic interventions are among the most effective methods of risk reduction in modern medicine. Despite its important contributions to reducing risk, the prophylactic method remains partially unknown due to the ethical, social, and psychological consequences it arises for individuals. Therefore, the prophylactic method can cause ethical and legal problems for individuals who need to assume the risk of uncertainty and genetic risk. Therefore, in the case of a prophylactic method that is based on the potential risk and which can have severe consequences for individuals, current medical standards should be more rigorously taken into account, considering the features particular to this method. More attention should be paid to protecting the patient's confidentiality. At the same time, an appropriate illumination should be performed to the nature of the method. It should also be noted that obtaining consent for the intervention and the obligation of indication should be carefully approached within the concrete data framework.

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37 Psychiatric Aspects of Prophylactic Surgery in Adults

Semra Etyemez and William W. Eaton

37.1 Introduction

This chapter describes the role of mental health in prophylactic surgery in adults. It begins with a presentation of the prevalence of mental disorder, followed by a discussion of risk factors for psychosocial distress and mental disorders. It describes the Angelina Jolie effect, the psychosocial impact of genetic testing, and highlights the impact of the prophylactic surgery on psychosocial health. The chapter closes with an overview of psychiatric assessment and treatment of patients undergoing surgery.

37.2 Epidemiology of Mental Disorders

Mental disorders are common worldwide and affect individuals' cognitive, behavioral, emotional, and physical well-being. A systematic review and meta-analysis of the literature from 1980 to 2013 reported a prevalence of mental disorders in adults during a 12-month period as approximately 18% and the lifetime prevalence as 29% [1, 2]. Worldwide, one in five adults experiences a mental disorder in a given year. Gender differences in psychiatric disorders are also reported; studies indicate that mood disorders and anxiety disorders are more common in females, whereas substance use disorders, attention-deficit hyperactive disorder (ADHD), and autism spectrum disorders are more common in males [1, 3–5]. Individuals with mental disorders are at higher risks of comorbid medical conditions [6–9]. Also, the risk of developing a subsequent mental disorder is increased in individuals with one mental disorder [10, 11]. Several risk factors for onset of mental disorders, including biological, psychosocial, socioeconomic, and environmental factors, have been investigated and identified [12–15]. Among these risk factors, experiencing early-life adverse events with physical, psychological and emotional neglect, trauma, chronic stress, and physical illnesses are the most important factors making an individual vulnerable for developing psychiatric disorders over one's life course. Similarly, family members of patients with chronic illnesses, such as cancer, experience psychological distress and are at elevated risk for developing mental disorders [16, 17]. The prevalence of depression and anxiety among family caregivers of cancer patients is remarkably high, estimated at 42% for depression and 47% for anxiety [16, 18].

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37.3 Physical Illnesses as Risk Factors for Psychological Distress

In the last decade, there has been an increased public awareness of genetic testing for severe illnesses such as cancer, and there is strong evidence that uptake of cancer screening is less likely among individuals with mental illness [19–22]. Additionally, many studies report a higher risk for cancer and higher mortality rates in individuals with mental illnesses compared to the general population [23–26]. Genetic testing to identify one's risk for complex diseases has psychiatric implications, and the mental health needs of the population undergoing a genetic test should be considered. The literature is limited regarding whether there are different genetic testing rates among those with or without mental illness. One study examined the effect of psychiatric disorders on genetic screening for breast and ovarian cancer and found no association between genetic cancer screening and coexisting psychiatric disorders [27]. Further, there have been several studies showing that individuals with underlying risk factors are at higher risk of experiencing psychological distress during the genetic testing process, and they are at higher risk of psychiatric complications. Distress at the baseline of the testing process, a history for psychiatric disorders, psychopharmacotherapy, use of a passive coping style, inaccurate risk perceptions, the experience of the death of a family member due to an inheritable cancer, complicated grief, being the first person in the family or group who undergoes genetic testing, and women having children are potential risk factors for psychiatric complications and long-term distress after the testing and surgical procedures [28, 29].

37.4 Angelina Jolie Effect

On May 14, 2013, Angelina Jolie disclosed that she had undergone a prophylactic mastectomy (PM) and bilateral salpingo-oophorectomy, due to a family history of cancer and being a *BRCA1* gene mutation carrier. This announcement had a remarkable impact on public awareness about prophylactic surgery, and this topic has garnered much attention for researchers. A systematic review investigated the impact of the "Angelina Jolie effect" on referrals, patients' attitudes, and decisions about genetic testing and risk-reducing mastectomies [30]. A significant increase of referrals for breast and ovarian cancer and genetic testing of *BRCA* status was reported, but no significant increase of risk-reducing surgery was observed [30]. Another important study conducted with 2572 adults demonstrated that 75% of participants were informed accurately about Angelina Jolie's risk for developing breast cancer, but only 10% of those 75% had sufficient knowledge about the risk of developing cancer in *BRCA* mutation carriers and in the general population [31]. Thus, although Angelina Jolie's story increased awareness of, and interest in, genetic testing for cancer and prophylactic surgery, there remains a lack of accurate understanding about the risk factors and treatment information for patients at high risk for hereditary cancer. This raises the need for understanding the psychosocial impact of genetic testing and prophylactic surgery, which has a significant impact on diagnosis, treatment, and outcomes of patients.

37.5 Psychosocial Impact of Genetic Testing

Although many are concerned about the negative mental health consequences of knowing one carries a mutation raising risk for cancer, the majority of individuals at high risk for cancer don't experience negative mental health consequences from genetic testing [32–34]. The prevalence of distress varies in several studies for different diseases; several investigators have reported that approximately 6–24% of individuals undergoing predictive genetic testing for hereditary breast and ovarian cancer (HBOC), hereditary nonpolyposis colon cancer (HNPCC), and Li-Fraumeni syndrome, presented elevated distress levels [29].

Also, a significant percentage of individuals with familial adenomatous polyposis (FAP) undergoing genetic testing suffer from distress and anxiety symptoms [29]. The majority of studies found that depressive and anxiety symptoms decrease considerably after the disclosure of results of gene testing in breast and ovarian cancer in both gene carriers and non-carriers [28]. On the other hand, depressive and anxiety symptoms increase after positive genetic results for Huntington disease, whereas no significant increase of these symptoms occur in Alzheimer disease and cardiovascular diseases after genetic testing [28].

Anxiety about potential psychological effects of genetic test results have implications in decision-making throughout the genetic testing process. There have been indications that one in three individuals coming from high-risk cancer families may decline or defer a genetic test [35, 36]. It has been reported that approximately one in two women coming from high-risk breast and ovarian cancer families did not follow up with genetic counseling sessions after the first session, and 36.3% of those declining genetic testing reported being concerned with the psychological consequences of the test outcome [37]. Being afraid of the negative impacts of the test results was one prevalent explanation for withdrawal after the first genetic counseling session [38]. Depression was also correlated with reduced uptake of HNPCC testing, as well as with delaying genetic testing; depression among people who delayed genetic testing for HBOC was consistently high at baseline and during 1- and 6-month follow-up periods [38, 39]. It has been reported that depression is a predictor for not undergoing genetic testing as well as withdrawal from *BRCA1/2* testing [40].

Psychological factors affect the decision-making process as well as adherence to recommended risk-reduction plans after a positive test. Studies have explored adherence to potential risk-reduction strategies and found that the majority of HNPCC mutation carriers (60–70%) were adherent to the recommended screenings guidelines compared to 10–15% of noncarriers of HNPCC mutation [41]. Also, HNPCC mutation carriers who were adherent to recommended colonoscopy guidelines were less likely to have depressive symptoms than noncarriers [42]. Communication about cancer risk, involvement of the family and encouragement for screening were important predictors of increased compliance to the recommended screening [43]. There was also a correlation between genetic test results and adherence rates to screening guidelines in *BRCA1/BRCA2* carriers. Significantly, higher rates of mammography uptake, but lower rates in adherence to ovarian cancer screening guidelines in *BRCA1/BRCA2* carriers than noncarriers are reported [44].

37.6 Impact of Prophylactic Surgery on Psychosocial Health

There have been indications that some psychiatric diagnoses are associated with undergoing prophylactic surgery. For instance, mood disorders, anxiety disorders, and schizophrenia, are associated with an elevated risk for undergoing hysterectomy, with and without concurrent bilateral oophorectomy for benign ovarian conditions [45, 46]. Preexisting somatoform disorders and personality disorders are associated with an increased risk of bilateral oophorectomy [46]. This study also reported that the risk of bilateral oophorectomy changed with age and psychiatric diagnosis; the odds ratio for adjustment disorders was considerably higher in ages 46–49, whereas odds ratio for mood disorders and anxiety disorders were significantly higher in those less than 45 years of age.

As with genetic testing, prophylactic surgeries also have psychosocial impacts on individuals who decide to undergo risk-reducing surgery. PM, oophorectomy, and bariatric surgery are invasive and irreversible interventions, which may affect individuals' mental health. One study reported that the majority of women undergoing (PM) were satisfied with the surgery outcome and reported decreased worry for cancer, but 9–25% of individuals described negative psychological and social impact of PM on emotional stability, level of stress, self-esteem, sexual rela-

tionship, and feelings of femininity [47]. Studies have reported a decrease of depression and anxiety symptoms in BRCA1/BRCA2 carriers after risk-reducing bilateral salpingo-oophorectomy (RRBSO) compared to these symptoms after cancer screening but before surgery [29, 48–50]. Nevertheless, studies didn't discuss the effect of age, education level, and occupation in the psychosocial consequences of the risk-reducing surgeries. One study conducted on younger women undergoing risk-reducing surgery with prophylactic mastectomy and oophorectomy reported no decrease in cancer worries [51]. Younger age at the prophylactic salpingo-oophorectomy was also correlated with lower social and sexual functioning, more endocrine impairments and increased anxiety [52]. Women with a loweducation level and no occupation are more likely to experience adverse effects of the prophylactic salpingo-oophorectomy [52]. Also, most women undergoing PM, RRBSO, or hysterectomy reported impairments in sexuality and libido [53]. Poor self-image, vaginal dryness, decrease in interest in sex, as well as change in interpersonal relationships are listed as reasons for reduced sexual activity [53]. Another striking finding was that 60–80% of BRCA1/BRCA2 carriers who underwent RRBSO reported that they did not receive any information about the availability of services for sex counseling, impact of surgery on self-image, and impact of surgery on sexual life as well as on their risk for cardiovascular disease [54]. These are important considerations for developing preintervention counseling. It seems that most of these women would have preferred receiving more information about the consequences of the surgical intervention before the procedure [54].

Psychosocial factors of individuals undergoing prophylactic bariatric surgery are also an important concern. Approximately, 40% of patients seeking bariatric surgery present with at least one mental health condition, such as depression, anxiety, BED, alcohol use disorder, or impulse control disorders [55]. A meta-analysis investigated the prevalence of psychiatric disorders among bariatric surgery candidates and recipients; the prevalence rates of any mood disorders reported were 23%, depression 19%, psychosis 1%, binge eating disorder (BED) 17%, anxiety 12%, suicidal ideation 9%, substance abuse disorders 3%, and PTSD 1% [56]. Another study investigating 8192 patients undergoing bariatric surgery reported that 57% of these patients had preoperative psychiatric disorders [57], thus, higher than the general population. There is ample evidence that bariatric surgery has a positive impact on psychopathology, quality of life, body image, socioeconomic status, and social relationships [58–61]. There is strong evidence of postoperative weight loss and maintenance after bariatric surgery [55, 60–62]. However, the weight loss is less in patients with depression and anxiety disorders compared to those without depression or anxiety [63]. A significant improvement in depressive symptoms is reported postoperatively, whereas no changes in anxiety is observed [63]. Nevertheless, over a longer term, depressive symptoms may reoccur and demonstrate increased depressive symptoms compared to preoperative levels [64–66]. The mood status of stable bipolar patients undergoing bariatric surgery does not seem to be altered [67]. Further, a reduction in suicide rates in bariatric surgery patients after surgery is also reported, however; the suicide rates still remain higher than the general population [68, 69]. Postoperative weight loss is less in patients with depression and anxiety disorders compared to those without depression or anxiety [63]. A significant improvement in cognitive function, such as memory and attention 1–3 years postsurgery, is also described in the literature [70, 71]. Cognitive functions are positively correlated with compliance to postoperative recommendations [72, 73].

As with depression and anxiety, eating disorders are common in patients seeking bariatric surgery. Binge eating disorder (BED) is defined by recurrent and frequent eating episodes with overeating, sense of loss of control, and embarrassment. Studies have shown that the prevalence of BED ranges between 10%–27% in patients seeking bariatric surgery [60, 61]. Postoperatively, a decrease in the prevalence of BED is reported, however some studies note the prevalence remained the same, that patients

exhibited "loss of control" eating and in some cases self-induced vomiting, which had adverse effects on weight loss and weight loss maintenance [60, 61]. Following bariatric surgery binge eating has been shown to be correlated with weight loss and emotional distress [74, 75]. The prevalence of night eating syndrome (NES), a condition characterized by evening hyperphagia, nocturnal eating, and morning anorexia is also higher in presurgical bariatric patients compared to the general population [76, 77] which appears to decrease after bariatric surgery [78]. Individuals after bariatric surgery are also at higher risk for developing alcohol use disorders [79]. An interesting finding is that individuals with Roux-en-Y gastric bypass demonstrated significantly higher rates of alcohol use compared to those with laparoscopic adjustable gastric banding (LAGB) [79]. Finally, Impulse Control Disorders (ICD) occur more frequently in individuals seeking bariatric surgery than the general population [61]. Excessive exercising to prevent weight gain, and occurrence or re-occurrence of ICD after bariatric surgery, are observed in some cases [61, 80, 81].

37.7 Psychiatric Assessment and Treatment of Surgery Patients

This information underscores the necessity and benefits of incorporating other disciplines, such as psychiatrists, psychologists, and sexual health counselors, throughout the whole process (genetic testing, preoperative, postoperative) to identify individuals at risk for worse postsurgical outcomes, to prevent adverse effects of the intervention, and to provide specific personalized treatment for each individual. Considering the high psychiatric comorbidity and its effect on outcomes of prophylactic surgery patients, a multimodal medical approach, including a comprehensive psychiatric assessment, is recommended along the course of genetic counseling, preoperative, and postoperative process. During the genetic testing process, patients should be screened for underlying risk factors and acute psychiatric disorders, and reevaluation of the mental status as well as the need for psychological and psychiatric support must be considered in every stage of the process.

Underestimating the impact of the mental status during the process of prophylactic surgery is a fundamental medical malpractice. The presence of mental illness, such as acute psychosis, major depression, bipolar disorder, active substance abuse, eating disorders, cancer phobia, or body dysmorphic syndrome, may affect the cognitive functions of individuals, influence decision-making, and impair postsurgical outcomes. If an untreated or inadequately managed psychiatric illness is present in individuals seeking prophylactic surgery, the surgery should be moved forward only after the acute severe mental illness is treated and stable. The presence of acute severe mental illness can lead to flawed decisions due to the lack of understanding the risks, consequences, pre and postoperative guidelines, which may lead to denying clearance for surgery, delay and denial of the procedures, and nonadherence to the recommended care after surgery [61]. In addition to the treatment of psychiatric comorbidities, preoperative assessment should also include considering potential interactions between psychopharmacological treatment and anesthetics to avoid peri and postoperative complications.

Discontinuation or dose reduction of any psychotropic drug should be done under psychiatric supervision to prevent relapse or an exacerbation of psychiatric symptoms. Continuing antidepressive treatments, mood stabilizers, and antipsychotic medication are recommended to prevent serotonin discontinuation syndrome, exacerbation of a depressive, manic, mixed, and psychotic episode. However, attention should be paid to the pharmacological management since several emergencies related to psychotropic drug actions can occur. For instance, among anti-depressive agents, particular attention should be given to monoamine oxidase inhibitors (MAOIs) due to high interaction potential with anesthetics and analgesics. Also, depressive patients taking selective serotonin reuptake inhibitors are at risk

for developing serotonin syndrome, characterized by excitement or confusion, excessive neuromuscular activity, and autonomic instability, which can be a fatal condition if untreated. Lithium serum level as well as the individual's clinical status should be monitored to avoid lithium toxicity with seizures, delirium, coma, and arrhythmias. Fluid, electrolytes, and renal function of patients taking lithium should be checked closely to avoid dyselectrolytemia. In addition, patients taking antipsychotics are at risk for neuroleptic malignant syndrome (NMS), usually found in a phase of early treatment, which is a life-threating condition defined by acute hyperpyrexia, muscle rigidity, and autonomic instability. Also, electrocardiographic abnormalities commonly occur in patients taking antipsychotic drugs; therefore, anesthetics, which have electrocardiographic side effects, should be avoided to prevent arrhythmia.

Postoperative monitoring of mental status must also be undertaken since psychiatric complications, such as postoperative cognitive impairment, postoperative delirium (hypoactive, hyperactive), adjustment disorder, postoperative depression, posttraumatic stress disorder related to surgery, and substance use, are often encountered. Each of the listed postoperative psychiatric complications requires clinical attention, and pharmacological and/or psychotherapy treatment may be required [61, 82]. Postoperative pain can also cause severe psychological distress and may require an individualized multimodal pain management plan, including pharmacological and nonpharmacological treatment. Careful attention should be paid to postoperative management of psychopharmacological treatment of patients undergoing bariatric surgery. Anatomic alterations due to the bariatric surgery significantly influence the pharmacokinetic effects as well as the overall effectiveness of the medications, which should be monitored with caution to detect ineffectiveness and prevent side effects and intoxication [82–84]. Monitoring medication blood level pre and postoperatively, adjusting medication doses, and if necessary, changing psychotropics to an immediate-release or parenteral formulation is recommended [82].

37.8 Conclusion

This chapter provided an overview of psychiatric aspects of prophylactic surgery. The scope of this chapter does not allow us to elaborate on each potential psychiatric disorder and its treatment and to cover all the relevant aspects of the perioperative process. More details can be found in the work of Zimbrean et al. on *Perioperative Psychiatry* [82]. This chapter has made it clear that throughout the genetic testing, preoperative and postoperative process for surgery, psychiatric assessment is critical to identify psychosocial risk factors and the psychiatric comorbidities, which may have a significant impact on the decision-making, treatment, complications, and postsurgical outcomes of the patient.

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Child and Adolescent Aspects in Prophylactic Surgery

38

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38.1 Introduction

The child and adolescent psychiatric approach takes into account [1]:

- Disorder patterns, including comorbid mental and physical diseases.
- The psychological, social, and biological state of development.
- Age.
- Coping with the different developmental tasks, for example, assuming individual responsibility versus parental dependence.
- Previous formative life events.
- Individual strengths and resources of the patient.
- Current or planned living environment (family, residential group, peer group, etc.)
- Disturbances in the living environment (e.g., children of mentally ill parents).
- The persons in the environment of the formative life events.
- Resources of the environment, including the willingness to give the patient personal responsibility without overburdening him/her (family, partner, friends, school, training, or workplace).
- Responsibilities of the environment (e.g., shared custody of separated parents).
- Order situation.
- Cultural background (e.g., migration).
- Available treatment resources.
- Time available.
- Experience of the parties concerned.
- Preferences of the patient and his/her family.

Developmental psychological effects, impact of psychiatric disorders, interactions between psychopharmacological treatment and anesthetics, family issues and further factors, which should be considered in the pre, peri and postoperative process, and the possible long-term effects will be presented.

38.2 Reasons for Child and Adolescent Psychiatric Interventions

Mental health problems affect 10–20% of children and adolescents. Different exposures to risk and protective factors, cultural context and methodological approaches contribute to difference of frequencies [2].

A systematic review of the psychosocial experiences of children undergoing surgery showed a strong association with preoperative anxiety and increased pain and behavioral disturbances up to 1 year after the surgery. Parents' and children's experiences are highly interconnected [3].

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Reevaluation of the mental status as well as the need for child and adolescent psychiatric support must be considered in every stage of the process. Both the surgery itself and the illness for which surgery is indicated can engender a great deal of distress in pediatric patients and their caregivers, which calls for a developmentally informed approach [4]. Another reason is that psychiatric comorbidities themselves can affect the outcomes of prophylactic surgery patients. Mental illness can affect the cognitive functions, influence decision-making and impair postsurgical outcomes. If an inadequately treated psychiatric illness is present in individuals or family seeking prophylactic surgery, the surgery should be moved forward only after the mental illness is adequately treated. Postoperative monitoring of mental status must also be undertaken since child and adolescent psychiatric complications similar to those in adults (See Chap. 37) can occur.

Genetic testing of the child is often the consequence of diagnosing a parent's cancer. Some of these children are at risk for emotional and behavioral problems. The child's age, their stage of psychological development at the time of diagnosis and disease, and family characteristics modify the psychological burden. Still, up to 25% of children experiencing severe parental illness will experience lowered and/or anxious mood, sleep problems, poor concentration, or difficulties at school. In worst-case scenarios, severe parental illness may cause profound trauma with consequences for later psychosocial functioning [5].

38.3 The Concept of Illness in Children

The fear of the unknown is independent of age. The unknown such as diseases, hospitalization and surgical procedures can cause anxiety in children and adolescents, which is pretty common and actually a healthy response. Besides that, separation from parents and pain induces anxiety in children and parents. Via indirect transference, parents' anxiety can cause more preoperative anxiety in children. High-preoperative anxiety leads to a need for higher doses of sedatives and anesthetics, which can increase risks associated with surgery. Anxiety can also enhance the experience of postoperative pain and may lead to receipt of more pain medication, decreased physical activity and slowed respirations, and ultimately increased pulmonary risks. Less activity can also result in an increased risk of deep vein thrombosis and reduced bowel transit [4].

It is important to consider how children understand illness and surgical procedures to minimize their level of anxiety. The cognitive developmental stage of children helps us to comprehend how they conceptualize and adapt to illness. Between 0 and 2 ages children are in a prelogical stage and depend on caregivers for their psychological and physical needs. Separation from caregivers is a principal stressor prior to a surgical procedure, and they may also develop anxiety from unfamiliar faces and white coats. Age 2–7 years is a preoperational stage with lots of fantasy thinking. They do not have logical thoughts but are able to understand simplistic concepts, such as cause and effect. Children are familiar with parts of their body but don't understand subtler physiological phenomena. This way of thinking may lead children to believe that a visit to a doctor means getting painful shots. Age 7–11 years is an operational stage. The child attains abstract thinking, hypothetical and deductive reasoning. Their logic is usually limited to a singular etiology, which can result in fearful misunderstanding. Many children still believe that surgery is a punishment for misconduct. This should be discussed openly with the child because they tend not to talk about that. Formal operational stage is from the age of 11. They can think abstractly and understand the processes of disease with multiple etiologies. Lack of privacy becomes an important issue. Children/adolescents and their parents should be prepared for medical procedures to reduce the anxiety and emotional distress. And also, healthcare providers should be aware of the psychological aspect [4].

38.4 Family Issues

Quality of the experience of a child or adolescent affected by prophylactic surgery correlates closely with the quality of experience of the (affected or unaffected) parents. Prophylactic surgical measures for a parent can lead to psychological impairments in the child or adolescent. The child's age, stage of psychological development at the time of diagnosis and disease, and family characteristics modify the psychological burden. In most cases, it makes sense to involve family members in diagnostics and therapy.

Among other things, the following behavioral disorders may indicate a need for assistance [6]:

- Largely continuous joylessness, even if a certain degree is understandable due to the strain.
- Difficulty falling asleep or sleeping through.
- Exhaustion.
- Pain due to above average physical strain or without somatic cause.
- Social withdrawal.
- Excessive anxieties.
- Feelings of guilt.
- Problems of concentration.
- Drop in performance at school.
- Increasing absenteeism.
- Self-harming behavior.
- Suicidal thoughts.

38.5 Shared Decision-Making

Informed consent with parental permission and assent of the child is an active process. Developmental maturation allows for increasing inclusion of the child's opinion in medical decision-making [7]. Young children lack decision-making capacity to a certain degree, so decisions about genetic testing must be conducted through surrogates, usually the parents, and must intend to place the child's welfare foremost in medical decision-making. Surrogate decision-making is also an ethically freighted concept, because although parents are the appropriate surrogates for their children in almost all cases, controversies arise when parents make decisions that seem contrary to the best interest of their child.

An adolescent in puberty often struggles for individuation, that is, the formation of individual identity and psychological boundaries, which enables differentiation and development in family and society, as an essential process in growing up. This may lead him to make decisions based on this principle, possibly also in opposition to his parents (and not necessarily based on reasonable health considerations). On the other hand, this effort at individuation may lead the young person to make a healthier decision than their parents [7].

The presence of mental illness of the child, the adolescent or/and the parent(s) can lead to flawed decisions due to the lack of understanding the risks and consequences, which may lead to denying clearance for surgery, delay and denial of the procedures, and nonadherence to the recommended care after surgery [8].

38.6 Perioperative Reactions and Disorders

Common perioperative child and adolescent psychiatric conditions are anxiety, depression and aggression/agitation [4]. All these symptoms can occur as adverse reactions of drugs used in connection with the operation, as a result of the perioperative process or as a combination. For example, narcotics can trigger fear, depressive moods, fatigue, delusion or hallucinations. Delirium-causing drugs include anesthetics, antibiotics, antihistamines, cardiovascular drugs and antihypertensives, contrast media, or nonsteroidal anti-inflammatory drugs [9]. Anxiety, depression, and aggressive disorders as well as other behavioral disorders can also exist etiologically independent as comorbid diseases. Interactions between all three causes occur frequently. Anxiety regarding surgery and associated behavioral responses differ based on child

age and stage of development. Pediatric delirium is an under recognized, but serious disorder present in many postoperative patients. Delir affects both consciousness and cognition with the cardinal features being acute change in mental status that tends to fluctuate, impaired attention, reduced awareness of one's environment, and appreciable cognitive impairment. The reported incidence of pediatric delirium is 10–80%, emerging after anesthesia and/or continuing until recovery period, perhaps not associated with anesthesia. Typical symptoms are agitation with kicking, absence of eye contact, inconsolability, and absence of awareness of surroundings [4].

In addition to treatment of psychiatric comorbidities, preoperative assessment should also include considering interactions between psychopharmacological treatment and anesthetics to avoid peri and postoperative complications. Discontinuation or dose reduction of any psychotropic drug should be done under child and adolescent psychiatric supervision to prevent a relapse or exacerbation of psychiatric symptoms. The risk of developing a serotonin syndrome or a malignant neuroleptic syndrome is present in children as well as in adults. The same applies to electrocardiographic abnormalities caused by psychotropic drugs (See Chap. 37).

38.7 Child and Adolescent Therapy

38.7.1 Psychopharmacotherapy

Many active ingredients used in adults have also been shown to work in older adolescents, but not necessarily in children. Children are not small adults, so the dosage can be very different from that of adults. In addition, many substances are not approved for children, so that off-label use may be required. For example, SSRIs have an antidepressant effect in children, but not tricyclic antidepressants. The scope of this chapter does not allow us to elaborate on each potential child and adolescent psychiatric disease and its psychopharmacotherapeutic treatment. Therefore, we refer to [10] for further information.

38.7.2 Psychotherapy

Past experiences, child's personality, age, developmental stage, gender, and the ability of the family to adapt to the situation affect the child's psychosocial adaptation. The personality of children and adolescents (such as cognitive and psychosocial skills, problem-solving skills, and coping strategies) can have a negative or positive impact on vulnerability, as well as contribute to resistance and the ability to compensate. The medical-psychological support covers from counseling, training programs for children/adolescence and parents, psychological prevention (like reducing anxiety of diagnosis and treatment methods through prior preparation and training) to group therapy for children/adolescence and parents, different various forms of individual psychotherapy for children/adolescence and parents, couple therapy, and family therapy [11]. It is now known that the parent-child relationship helps the child deal with the disease in the long-term. The affected parent is also a key person in providing information to an affected child [12].

38.7.3 Other Psychosocial Interventions

In addition to pediatric psychological or psychiatric interventions, school-related and/or activity-related therapy approaches in occupational therapy, movement therapy, art therapy, or music therapy can support recovery not only with regard to sensomotoric and neuropsychological functions, but also with regard to emotional and social [13].

In addition, general social services or the youth welfare office can provide assistance in the

domestic environment of the child or adolescent for psychosocial reintegration. The involvement of the school is also useful.

38.8 Cancer-Related Aspects

38.8.1 Psychological Effects of Genetic Testing for Cancer in Children and Adolescents

There are concerns about predictive genetic testing of minors for several reasons. First, it removes the individual's right to make an autonomous decision to be tested as an intellectually competent adult. Second, it denies them the right to confidentiality of results from parents and other family members. Third, identification of a minor as carrying a mutation has the potential for adverse emotional and psychological impact on the child [14].

Some individuals respond negatively to the test results and experience increased anxiety due to concerns regarding the test not identifying all possible gene mutations. In addition, others experience the guilt of survivors, or parents experience the guilt of having passed the mutation on to their child [15].

The fear of possible psychological effects of genetic test results has implications for decision-making throughout the genetic testing process. About one-third of those who refuse genetic testing are concerned about the psychological consequences of the test result. One in three people from high-risk cancer families refuse or postpone a genetic test. Depression is a predictor for not undergoing genetic testing. Talking about the cancer risk, involving the family and encouraging to screening are important for good adherence to recommended screening (See Chap. 37).

Testing healthy children and adolescents for genetic disorders may harm parent-child bonds or the child's self-concept. Clinicians encounter situations where they must weigh the child's or adolescent's wishes against wishes of parents. Most studies suggest that there are no significant changes in psychosocial well-being in children who received a genetic test result. However, Wade et al. (2010) reported that this lack of impact may be because of methodological weaknesses in quantitative studies. The most adverse findings were relatively high levels of worry and possible influence children's perspectives on future partner selection and parental roles [16].

Many children and their families create narratives about a child's genetic status: Some families assume that their children are destined to have, or not have, the familial condition. The baseline uncertainty about risk status can cause psychosocial distress in the absence of genetic testing.

The American Society of Human Genetics (ASHG) offers the following recommendations [17]:

- Unless there is a clinical intervention appropriate in childhood, parents should be encouraged to defer predictive or predispositional testing for adult-onset conditions until adulthood or at least until the child is an older adolescent who can participate in decision-making in a relatively mature manner.
- Adolescents should be encouraged to defer predictive or predispositional testing for adult-onset conditions until adulthood because of the complexity of the potential impact of the information at formative life stages.
- Providers should offer to explore the reasons why parents or adolescents are interested in predictive or predispositional testing for adult-onset conditions. Providers can acknowledge that, in some cases, testing might be a reasonable decision, but decisions should follow thorough deliberation.

Adolescents should be provided the opportunity to discuss these issues without the presence of their parents, although parents should be involved in, and supportive of, final decisions for testing. A referral to genetic counselors and mental-health professionals is appropriate if the clinician and family need additional support for decision-making or in assessing the psychosocial dynamics.

Deferring testing to adulthood allows children the opportunity to make their own decisions. This is especially important for the small subset of conditions, where a minority of at-risk adults opt for genetic testing, such as for Huntington disease. The ASHG offers the following recommendations:

- Facilitating predictive or predispositional testing of children for adult-onset conditions can be justified in certain circumstances. For example, after careful deliberations with the family and older child, testing can be justified to alleviate substantial psychosocial distress or to facilitate specific life-planning decisions.
- The impact of predictive testing on children and families remains uncertain and, therefore, can be justified in specific cases when it is requested by families after informed deliberations and when the testing is not clearly inconsistent with the welfare of the child.

In the study of Codori et al. (1996), 41 children aged 6–16 years were followed up for 3 months after genetic testing [18]. The mutation-positive group with affected mothers showed increased depression scores at follow-up. The mutation-negative groups did not change, regardless of sex of the affected parent and time of assessment. Regardless of their test results, the groups with affected fathers had a significant decrease in anxiety scores at follow-up, and those with affected mothers had a significant increase. Depression, anxiety, and behavioral problems and competence scores remained in the normal range at follow-up. Anecdotal information suggests that children's overall favorable reactions may be attributable to their parents' views of the disease as a treatable disease. Alternatively, the mutation-positive children may not be reporting clinically significant increases in distress because they do not understand the implications of the genetic diagnosis. In a post-hoc test of this hypothesis, correlations between age (a possible marker for comprehension) and distress (depression, anxiety, and behavior problems) found no significant association.

38.8.2 Familial Adenomatous Polyposis (FAP)

FAP is an inherited condition characterized by numerous polyps in the large intestine but may also be found in the stomach and small intestine. If unrecognized and left untreated, this disorder leads to colon cancer. *Adenomatous polyposis coli* (*APC)* is a tumor suppressor gene located on 5q21–22, a site reported to also be associated with schizophrenia [18]. Duodenal cancer is the second leading cause of cancer deaths in patients with FAP. The other organs that form tumors include: skin, bones, eyes, thyroid, and abdomen [19]. Some patients are at increased risk for brain tumors, including cerebellar medulloblastomas [15].

Colectomy is recommended after adenomas emerge. Prophylactic surgery may be recommended before the age of 25 or upon detection if actively monitored. When the rectum is involved, the rectum and part or all the colon are removed [20]. The patient may require an ileostomy, which is a permanent stoma, where stool goes into a bag from the abdomen, or they may have ileoanal pouch reconstruction. The decision to remove the colon is based on the amount of polyps in the rectum as well as the family history [21].

Because of these interventions, patients begin to have difficulty with medication absorption. Careful consideration has to be made when deciding medications, taking into consideration side effect profile. When the patient develops polyps in the duodenum or part of the stomach and undergoes resection, they may have more difficulty absorbing medication. In mentally ill patients, specifically those who require psychotropic medication, there must be a mindful consideration of the type of medication prescribed and how it will be absorbed. The treating psychiatrist may consider using long-acting injectable medications rather than oral modalities [15].

Counseling is recommended for all patients and their family members. Benefits include helping a person understand and cope with the anxiety and uncertainty of testing. Counselors can assist in the decision process regarding testing, screening, and interventions. Fear of discrimina-

tion in the work force or school due to physical limitations, as well as issues with body image and self-esteem, can be discussed and addressed by clinicians. Counseling should be provided on an ongoing basis.

The initial genetic testing and counseling may have been done at a time when the child/adolescent may not have had the ability to process the scope of the illness and its complications. It has been found that those who have had genetic counseling at an early age, recall only approximately two-thirds of the medical information presented [22].

Genetic counseling for individuals with chronic mental illness can present with even more challenges. For clinicians, it is especially important to establish rapport and encourage compliance, since they may be less likely to actively seek out referral or be unwilling to believe the information provided [23]. FAP-support groups are available and provide a venue for patients and family members to share information. But few groups focus on assisting those with comorbid mental illness [15].

38.8.2.1 Recommendations for Counseling a Patient with Mental Illness and FAP

- Do not overload a psychiatric patient with excessive information during a period when that person is not stable or when they may have limited understanding of the illness and its implications.
- Screening for new symptoms as well as monitoring for substance use is recommended, particularly upon initiating genetic counseling.
- Exploring patients' feelings about living with the potential threat of developing cancer or adjustment to a possible premature death or loss of relatives affected with cancer is recommended.

38.8.2.2 Psychiatric Aspects

Barber et al. [24] reported about a patient with FAP coli, carcinoma of the rectum, mental retardation, autism, and minor dysmorphic features. Further studies have shown that FAP in one family member may lead to a high level of mental health problems in other members of the family, particularly adolescents, including oppositional defiant disorder, adjustment disorder, major depression, and anxiety disorder [25].

38.8.2.3 Schizophrenia

One gene associated with schizophrenia has been the *APC* gene, a tumor suppressor gene that increases one's risk for FAP [26]. Gonzalez et al. [15] present a female with schizophrenia, where FAP was diagnosed at the age of 17. The patient's mother deceased from colon cancer secondary to FAP also suffered from schizophrenia. Her mother, mother's twin, and grandparent have also suffered from this familial colon cancer syndrome, as does her older brother. Her mother's twin and older brother underwent prophylactic colectomy. The mother died from colon cancer when the patient was 15, and her aunt became her legal guardian. The patient's older brother also possesses the *APC* gene mutation and underwent prophylactic surgery. The patient's maternal aunt and mother's identical twin had undergone multiple surgeries. Her mother, her mother's twin, and a grandparent reportedly suffered from mental illness [15].

38.8.3 Hereditary Breast and Ovarian Cancer (HBOC)

Norris et al. [27] explored in their study the communication and decision-making strategies of five families with hereditary breast and ovarian cancer (HBOC) risk. Investigators asked female carriers of *BRCA1* and *BRCA2* genetic mutations to recall early knowledge and experiences concerning cancer risk. Husbands and children (aged 15–25 years) of women with HBOC risk also were interviewed on knowledge, experiences, and expectations for future decisions regarding their risk. Nurses should assess patients and their families for issues with body image and adjustment after cancer treatment and offer appropriate support. In addition, parents should be advised on when and how to tell children about their potential risk and support their testing and health-promotion decisions [27].

Children of parents with mutations (*BRCA1/BRCA2*) have a 50% chance of inheriting them. Many mothers assume that disclosure of genetic risk to children will cause distress depression, withdrawal, and may affect the child's sense of security and consistently reported fear about communicating genetic testing information with their adolescent daughters [28]. It seems important to support the mothers about how to talk cancer risk information to their adolescent daughters and how much information is sufficient to communicate. If needed, mothers can consult an expert and support their daughters to receive counseling.

38.8.4 Medullary Thyroid Cancer (MTC)

MTC is generally the first manifestation of MEN2A syndrome and develops usually before age 6 and sometimes before age 2. MEN2A is a highly penetrant, autosomal-dominant endocrine tumor syndrome characterized by the development of cancer in >90%. MEN2B is characterized by the early development of an aggressive form of MTC, typically during the first year of life. Individuals with MEN2B are likely to develop metastatic MTC at an early age if they do not undergo prophylactic thyroidectomy before age 1. Genetic testing for hereditary MTC syndromes has had an enormous impact on reducing the incidence of MTC in the affected families. Prophylactic thyroidectomy is recommended for the children tested positive for the *RET* gene mutation at ages 0–1. Thyroidectomy in children is usually associated with a higher rate of complications, such as recurrent laryngeal nerve injury and hypoparathyroidism, as compared to the surgery in adults. All individuals who have undergone thyroidectomy need thyroid hormone replacement therapy along with annual screening for pheochromocytoma and hyperparathyroidism [29].

Thyroid hormone replacement in children has some challenges. While children are not likely to complain of decreased energy, concerned parents may tend to transfer their perception of what thyroid hormone should do to the child's activity level. The ability to achieve consistent TSH suppression in children can be difficult, mainly due to higher noncompliance rates with the medication. When the home environment is not conducive to compliance, other measures may need to be taken [30].

Underlying mental health problems, such as depression, personality disorders (e.g., borderline personality), and addictions, may complicate treatment of hypothyroidism and may impact perception of health state and adversely affect rational decision-making capacity. Patients in these categories should have an assessment by a child and adolescent psychiatrist or clinical child and adolescent psychologist to rule out underlying mental health conditions. In patients with persistent complaints of hypothyroidism as well as chronic pain and malaise, all organic causes should be ruled out, followed by referral to a mental health practitioner to screen for somatoform disorder [31].

It could be difficult identifying children at risk for inheriting MEN2 from a parent who refuses to disclose to the child their specific risks and the available preventative or therapeutic options. It may be necessary to involve state officials and the courts to resolve such issues in order to protect the child. With pediatric patients who have not reached the age of consent, it may be necessary for physicians to seek state intervention to prevent harm when there is parental refusal to inform their children of the risk of developing a malignant tumor [32].

38.9 Non-cancer-Related Aspects

38.9.1 Intestinal Malrotation

Malrotation is a result of an error in intestinal rotation and fixation of the intestinal mesentery. Most of the patients are symptomatic under age of 1, where 50% of patients are in the newborn period [33]. This anatomical deficit may cause midgut volvulus, followed by ischemic bowel,

possible short gut syndrome, and death. The sudden onset of the symptoms after volvulus is typical at this age with bilious vomiting, abdominal distension, abdominal tenderness, peritonitis indicating perforation, and rectal bleeding indicating bowel ischemia at later phase. In later childhood, the symptoms become more atypical like cyclic vomiting (often non-bilious), recurrent abdominal pain, and failure to thrive [34]. Therefore, the syndrome of cyclic vomiting, psychosomatic illnesses, and parental neglect must be considered from a differential diagnostic perspective [35].

38.9.2 Bariatric Surgery

Children with obesity often have a lowered self-esteem and an increased risk of being bullied [36], depressed quality of life, type 2 diabetes, obstructive sleep apnea, nonalcoholic steatohepatitis, hypertension, dyslipidemia, and carbohydrate intolerance. Binge eating disorder is the most common nutrition and eating disorder in pediatric obesity. It is an indication of psychopathology and a serious risk factor, especially in family obesity, negative experiences, and other factors predisposing to psychiatric disorders. Child and adolescent psychiatric counseling should be undertaken to identify cases at risk of psychotic disorders, major depression, personality or eating disorders, alcoholism, and drug dependence [37]. Children are given antipsychotics not only for psychoses, but also for aggressive behavior or Tourette's syndrome. They appear to be particularly vulnerable to antipsychotic-induced weight gain, regardless of taking olanzapine or aripiprazole. This is often due to increased appetite in the family and/or during puberty without sufficient physical activity. The effects of nutritional advice, exercise programs, cognitive, behavioral, and pharmacological interventions are moderate at best, but often insufficient, due to insufficient compliance [38]. According to the guidelines of the American Society for Metabolic and Bariatric Surgery [39], metabolic and bariatric surgery is safe and effective in adolescents.

In the postoperative follow-up anthropometric, clinical and nutritional, including child and adolescent psychiatric assessment and counseling, must be performed; early and late complications have to be monitored [36]. Attention is needed to postoperative management of psychopharmacological treatment of patients undergoing bariatric surgery. Anatomical changes caused by bariatric surgery influence the pharmacokinetics and the effectiveness of drugs, which can lead to ineffectiveness, side effects, and poisoning. Pre and postoperatively, the blood levels of the drugs must be monitored and the dosage adjusted if necessary [40]. There is strong evidence to support a considerable alteration of the gut microbiome after bariatric surgery [41]. The microbiome appears to influence many psychological processes and neuropsychiatric disorders, including mood and anxiety disorders, ADHD, and autism spectrum disorders. It is also likely that most psychotropic drugs have an influence on the microbiome [42].

38.10 Conclusion

Illnesses and medical procedures like surgery cause a lot of emotional stress in children and adolescents and their parents. With prophylactic surgery, other difficulties can show up like genetic testing and psychosocial dynamics in the decision-making process. Regardless of the disease and the operation to be performed, children and adolescents considering their development levels should be sufficiently informed and prepared about their illness, surgery, and perioperative procedures. Interaction between parents and children/adolescents is an important element by coping with disease and surgical processes. Psychiatric comorbidities in children/adolescents and their parents may have a significant impact on the decision-making, (lifelong) coping with illness, and postsurgical and psychosocial adaptation.

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39 Endoscopic Approaches for Prophylactic Purposes

Ömer Karahan and Barış Sevinç

39.1 Introduction

In recent years, depending on the improvement in endoscopic methods, endoscopic approaches have come to the fore in the diagnosis and treatment of many gastrointestinal pathologies. Advanced procedures like endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) allow prophylaxis and treatment of early cancers. In this chapter, endoscopic procedures used in prophylaxis are discussed in view of literature.

39.2 Endoscopic Ultrasonography (EUS)

Endoscopic ultrasonography (EUS) is used for interventions rather than diagnostic approach. Examples of EUS-guided procedures are blockage and neurolysis of celiac nerve plexus, drainage of pancreatic pseudocyst, drainage of intra-abdominal abscess, drainage of bile and pancreatic ducts, choledocoduodenostomy, hepaticogastrostomy and intratumoral injections [1–3].

EUS use is now considered as the gold standard for many gastrointestinal diseases, especially for pancreaticobiliary diseases. EUS-guided needle insertion allows access to remote lesions that were difficult to reach in the past [3].

EUS is associated with an overall decreased mortality rate, fewer major and long-term complications compared to surgery, especially in patients with pancreatic pseudocysts [4] (Fig. 39.1). EUS-guided biliary drainage is an alternative to radiological interventions and ERCP [4]. Biliary drainage can be performed as EUS-guided hepaticogastrostomy or choledochoduodenostomy [3, 4]. Moreover, drainage of intra-abdominal abscess or fluids through transesophageal, transgastric or transcolonic route is possible [5]. These advantages of EUS provide the possibility of avoidance from high-risk surgical procedures.

39.3 Endoscopic Polypectomy

Gastrointestinal system polyps are excised for both diagnosis and treatment. Removal of colonic polyps is an effective method in prevention of colorectal carcinoma. The features of the polyp, classification, ways for removal and histopathological evaluation are all discussed in guidelines. For determination of surface morphology, Paris classification can be used. Localization of the lesion, diameters and morphology are situated in endoscopy report. Lesions larger than 10 mm should be pictured [6].

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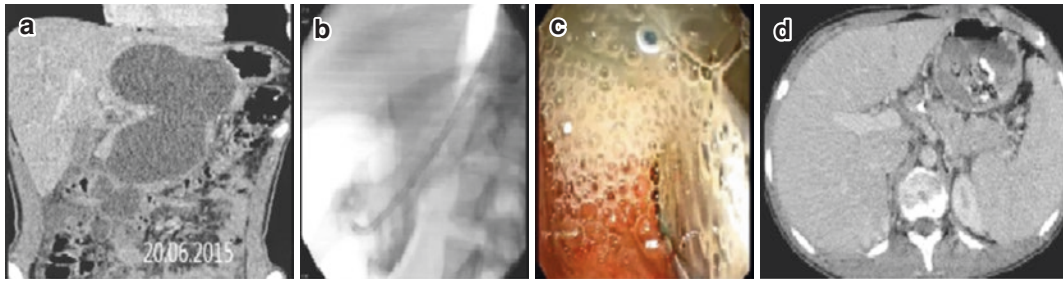

Fig. 39.1 Endoscopic drainage of pseudocyst; CT image of the pancreatic pseudocyst (**a**), radiological appearance of the stent placed in the pseudocyst (**b**), pseudocyst contents discharge into the duodenum (**c**) and CT image, 2 months after the procedure (**d**)

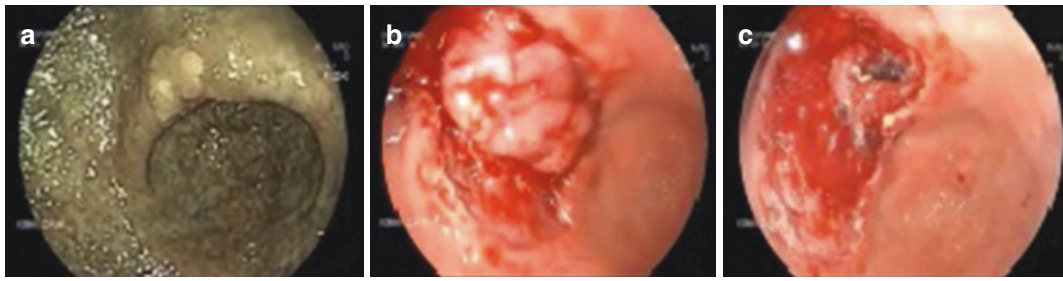

Fig. 39.2 ESD in early gastric cancer; FICE image of early gastric cancer (**a**), the lesion freed from its surroundings and from the floor (**b**) and tissue defect remaining after ESD is complete (**c**)

Excision of colorectal polyps by polypectomy decreases colorectal cancer incidence [7]. Moreover, polypectomy decreases the colorectal cancer-related death rate. Adenomatous polyps should be detected and removed endoscopically [8]. In pedunculated polyps, single polypectomy is sufficient. In sessile and large polyps, piecemeal polypectomy should be performed.

39.4 Endoscopic Mucosal Resection

Early gastric cancer that will be treated by EMR should be well- or moderately differentiated adenocarcinoma, macroscopically elevated or depressed superficial lesions and have no invasion or ulceration [9]. EMR is used in premalignant or early gastric cancer as well as in treatment of esophageal, duodenal and colonic lesions. In well-evaluated cases, EMR is a good alternative to surgical resection [10]. Endoscopic surveillance programs have been started to be applied by AGA for endoscopic eradication of dysplasia developed in Barrett's epithelium [11].

Endoscopic submucosal dissection (ESD) is an improved version of EMR. ESD mainly has three steps; first one is the elevation of mucosa by submucosal injection. Submucosal injection prevents damage to deeper structures and reduces the risk of perforation and hemorrhage. The second step is the cutting of healthy mucosa around the lesion. The last step is the resection of the lesion by dissection of connective tissue below the lesion (Fig. 39.2) [12].

As in EMR, before resection by ESD, the lesion should be carefully evaluated by endoscopy, EUS and histopathology for localization, invasion depth, ulceration and metastases. In early gastric cancer, results of ESD are compatible with the results of radical gastrectomy. The postprocedural comfort of the patient is better, and hospital stay is shorter in ESD [13].

Although, it is more challenging compared to stomach, benign, premalignant, malignant mucosal and submucosal lesions of esophagus, small

intestine and colon can be resected by ESD [14]. In selected patients, ESD has compatible oncologic outcomes compared to surgery with low mortality and morbidity rate [14, 15]. In some ESD series, most of the cases are composed of benign and premalignant lesions. This fact indicates that ESD is an important treatment modality as well as an important method for endoscopic prophylaxis [14].

In treatment of colonic lesions by ESD, en bloc resection rate is 82.8%, and perforation rate is 4.7%. Most of the perforations are so small that can be treated conservatively or by endoscopic clips application. The need for surgical intervention for perforation is very rare. In the near future, ESD will be widely used for early-stage colorectal cancers [16].

39.5 Radiofrequency Ablation (RFA)

Since Barrett's esophagus (BE) causes increased malignancy risk, for prevention of cancer formation, BE should be treated [17, 18]. One of the treatment options in BE is RFA. By RFA, neoplastic transition is prevented in cases with low-grade dysplasia [19]. Moreover, high-grade dysplasia can be safely treated by RFA [20]. In patients with dysplastic BE, both dysplasia and intestinal metaplasia can be completely eradicated by RFA, and the risk of progression is decreased [17]. Therefore, the risk of esophageal cancer development is reduced [19].

The combined endoscopic removal and RFA of the dysplasia safely and effectively treats the early esophageal neoplasia developed from BE [20].

Moreover, RFA of the lower esophageal sphincter significantly reduces the complaints of reflux. This feature of RFA can be an alternative to medical treatment and surgical fundoplication [18].

Another application area of endoscopic RFA is the palliation of malignant biliary strictures. In palliation of malignant biliary strictures, RFA is a reliable and safe method [21].

39.6 Endoscopic Treatment of Gastrointestinal Bleeding

The timing of endoscopy in GIS bleeding depends on the clinical condition. Emergent endoscopy (within 24 h) can be performed in the following: hematemesis in patient with a history of malignancy or cirrhosis, hypotension, tachycardia, shock, hemoglobin level below 8 g/dL [22]. Variceal and non-variceal bleeding (peptic ulcer, gastroduodenal erosions, Mallory-Weiss lesions, etc.), active bleeding and stopped bleeding should be evaluated separately. There are several applications like topical, injection, mechanical and thermal methods. There is no standard treatment method that can be applied to all cases [23]. In bleeding ulcers, endoscopic treatment is used for cases with active bleeding or cases with high risk of rebleeding. In cases that bleeding is controlled, there is no need for repeat endoscopy; whereas, in cases with rebleeding, repeat endoscopy is needed. In low-risk patients, endoscopy can be performed as outpatient manner [22]. In some cases, more than one method can be combined, or medical treatment can be added to increase the success rate of the treatment [24].

Endoscopic ligation of varices reduces the risk of bleeding and mortality [25]. Band ligation of esophageal varices reduces mortality, upper gastrointestinal bleeding, variceal bleeding and serious adverse events compared to no intervention. Prophylactic endoscopic treatment can be applied to patients who cannot tolerate beta-blocker treatment with large and medium varices [25, 26].

In high-risk patients with non-variceal upper GIS bleeding-combined endoscopic treatment with proton-pump inhibitors reduces both mortality and rebleeding risk [27].

In lower GIS bleeding caused by angiodysplasia, diverticulosis and polypectomy, the success rate of endoscopic treatment is about 92% [28]. Endoscopic treatment methods that can be used are diluted epinephrine injection, bipolar electrocoagulation, heater probe, clips application and band ligation [29, 30].

39.7 Endoscopic Treatment of Gastrointestinal Stenosis

Endoscopic balloon dilation of upper gastrointestinal stenosis is safe and effective [31, 32]. Endoscopic dilation combined with endoscopic incision increases the success rate in gastric outlet obstruction [33]. After esophagus resection that continuity is provided by stomach, there is no need for pyloric drainage procedures. Early and late outlet obstruction can be treated by endoscopic balloon dilation [34].

In untreatable malignant gastric outlet obstruction, duodenal stenting increases the quality of life [35]. In selected cases with benign obstruction, duodenal stenting can be used [36]. In benign small intestine and colonic stenosis, biodegradable stents can be applied easily [37].

As in other obstructions of the GIS, endoscopic treatment can be used in stenosis due to Crohn's disease [38]. In Crohn's disease, endoscopic balloon dilation of stenosis provides avoidance from surgery [39].

In colonic obstruction, stenting can provide elective surgery rather than emergency surgery. Moreover, in high-risk patients, it provides time for preparation to surgery. In emergency surgery, most of the procedures necessitate ostomy and two-step surgery. Stenting of the obstruction can provide one-step elective and even laparoscopic surgery. The success rate of self-expandable stents can be as high as 97.8% [40].

In treatment of benign biliary stenosis, single or multiple temporary stenting can be used [41]. In biliary stenosis after liver transplantation, endoscopic balloon dilation, followed by stenting with gradually increased diameters, is the treatment of choice [42].

39.8 ERCP

Nowadays, ERCP is used for therapeutic purposes rather than diagnosis. ERCP has a wide-usage area; treatment of bile duct stones, stenting of benign and malignant bile duct stenosis, treatment of Oddi sphincter dysfunction, palliation of neoplasia obstructing ampulla of Vater, treatment of bile fistula, sump syndrome and parasitic diseases of bile ducts.

Bile duct stones, smaller than 1 cm, can be treated endoscopically with a success rate of 85%. Most of the larger stones can also be extracted by using special devices and techniques [43]. Stones larger than 2 cm can be broken into pieces and extracted by balloon and basket catheter. Endoscopic treatment rate of large stones after mechanical lithotripsy is 79–98% [44, 45]. The complication rate of balloon extraction is lower than extraction with basket [46].

Adenoma of papilla Vater can be treated surgically by local excision. Mortality and morbidity rate of this procedure is lower than the Whipple procedure; however, higher than the endoscopic treatment. Therefore, endoscopic treatment of ampullary adenoma has better results. Ampullary adenomas up to 2 cm can be treated by endoscopic ampullectomy or endoscopic papillectomy. Surgical treatment should be chosen for adenomas with dysplasia or high risk for carcinoma. After endoscopic resection, adenomas can be followed endoscopically; however, if carcinoma exists, surgical excision should be performed [47].

In primary of metastatic tumors causing obstructive jaundice biliary drainage is needed. Biliary drainage even for palliation or preparation to surgery treats cholangitis; itching, nausea and anorexia improves; quality of life increases. It can provide palliation in cases with terminal-stage malignancy. In preparation to surgery, drainage should be performed when the time to surgery is more than 15 days; if there is cholangitis or bilirubin level is higher than 15 mg/dL. Biliary drainage can be provided by ERCP, endoscopic sphincterotomy and stenting or by percutaneous transhepatic cholangiography. EUS-guided biliary drainage is a good alternative to percutaneous procedures [48–50].

In cases with malignant bile duct obstruction rate of curative treatment is only 10–15%. The

rate of palliative treatment is very high. Self-expandable metallic stents (SEMSs) are used for palliation. Compared to plastic stents, SEMSs provide longer luminal patency period [51].

Rupture to biliary tree is an important complication of hydatid cyst. It can cause obstructive jaundice and cholangitis. Rupture missed preoperatively can cause postoperative complications like biliary fistula, biloma, infection of the cyst cavity and obstructive jaundice [52]. ERCP is indicated in postoperative biliary fistula and in cases with hydatid cyst membranes located in biliary tree. Biliary obstruction and cholangitis due to *Fasciola hepatica* and *Ascaris* are rare. The biliary obstruction caused by those parasites is also treated by ERCP [53–57].

ERCP is indicated in several pancreatic disorders like acute and chronic pancreatitis, pancreatic pseudocyst, pancreatic duct stones and obstruction. Endoscopic treatment aims to reduce pressure of papilla Vater in acute pancreatitis and to resolve pain in chronic pancreatitis (Fig. 39.3) [58–60]. Main duct obstruction, pancreatic cancer and pseudocyst may cause pancreatic pain. The aim of the treatment is to decrease the pressure in the pancreatic duct to resolve pain.

ERCP is a modality that gains wider usage area for both prophylaxis and treatment of some disorders, without advanced surgical procedures.

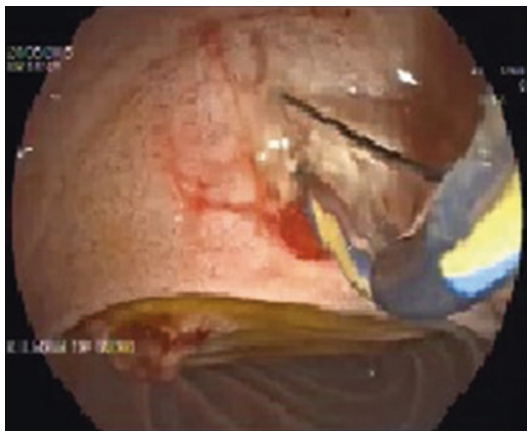

Fig. 39.3 Papilla cannulation and sphincterotomy with ERCP

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40 The Place of Prophylactic Surgery in Guidelines

Nihan Acar and Osman Nuri Dilek

40.1 Introduction

Guidelines are valuable sources to decide when and how to perform prophylactic surgery. Besides, they ensure to protect the patient from both overtreatment and delayed treatment in clinical or surgical practice, standardize the service provided, and also protect the physician/surgeon legally and ethically.

Latest and current guidelines on all fields of general surgery, which include recommendations regarding prophylactic, preventive and risk-reducing surgery, are going to be introduced and reviewed in this chapter (Table 40.1).

40.2 Thyroid and Parathyroid

The latest guideline published by the American Thyroid Association (ATA) on thyroid nodules and differentiated thyroid cancer was in 2015. Major concerns regarding prophylactic surgery were generally about the neck dissection. The authors evaluated the potential benefits and the necessity of prophylactic ipsilateral or bilateral, central-compartment, and lateral-compartment neck dissection [1]. The revised version of ATA guidelines for the management of medullary thyroid carcinoma, which was also published in 2015, adverted five criteria for prophylactic surgery in patients with hereditary cancer syndromes. Ultimately, they concluded that MEN2A and MEN2B met each criterion [2].

In the British thyroid association guidelines for the management of thyroid cancer from 2014, recommendations for prophylactic thyroidectomy in MEN syndromes and prophylactic neck dissection in differentiated thyroid cancers and medullary thyroid cancer were published [3]. They also emphasized that the risk of injury to the recurrent laryngeal nerves and parathyroid glands associated with prophylactic surgery should be considered.

Italian consensus on diagnosis and treatment of differentiated thyroid cancer, which includes joint statements of six Italian societies, was published in 2018. It also stated the same issues again as previous counterparts [4].

Chinese Association of Thyroid Oncology (CATO) and Chinese Anti-Cancer Association published Chinese expert consensus and guidelines for the diagnosis and treatment of papillary thyroid microcarcinoma in 2016. Unlike their western counterparts, they graded the recommendations from "A" to "I." However, they gave

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Table 40.1 Current guidelines subjecting prophylactic surgery

Guidelines	Year	Country/ region
*Thyroid and parathyroid****		
BTA guidelines for the management of thyroid cancer	2014	UK
ATA guidelines on thyroid nodules and differentiated thyroid cancer	2015	USA
ATA guidelines for the management of medullary thyroid carcinoma	2015	USA
CATO and Chinese anti-cancer association, Chinese expert consensus and guidelines for the diagnosis and treatment of papillary thyroid microcarcinoma	2016	China
AAES guidelines for definitive management of primary hyperparathyroidism	2016	USA
Italian consensus on diagnosis and treatment of differentiated thyroid cancer: Joint statements of six Italian societies	2018	Italy
NCCN clinical practice guidelines in thyroid cancer	2019	USA
AAES guidelines for the definitive surgical management of thyroid disease in adults	2020	USA
*Breast****		
Manchester guidelines for contralateral risk-reducing mastectomy	2015	UK
ESMO clinical practice guidelines for cancer prevention and screening in *BRCA* mutation carriers and other breast/ovarian hereditary cancer syndromes	2016	Europe
ASBrS consensus guideline on genetic testing for hereditary breast cancer	2019	USA
NCCN clinical practice guidelines: Breast cancer risk reduction	2019	USA
NCCN clinical practice guidelines in oncology: Breast cancer	2020	USA
NCCN genetic/familial high-risk assessment: Breast, ovarian, and pancreatic	2020	USA
*Adrenal glands****		
AACE and AAES medical guidelines for the management of adrenal incidentalomas	2009	USA
European Society of Endocrinology clinical practice guideline, in collaboration with the European network for the study of adrenal tumors	2016	Europe
Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: An endocrine society clinical practice guideline	2018	USA
*Upper gastrointestinal tract****		
AGA medical position statement on the management of Barrett's esophagus	2011	USA
ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes	2015	USA
Hereditary diffuse gastric cancer: Updated clinical guidelines with an emphasis on germline *CDH1* mutation carriers	2015	International
Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: ESGE guideline	2015	Europe
Guidelines for endoscopic management of nonvariceal upper gastrointestinal bleeding	2016	Japan
Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines	2018	Japan
ASMBS pediatric metabolic and bariatric surgery guidelines	2018	USA
European guidelines on achalasia: United European gastroenterology and European Society of Neurogastroenterology and motility recommendations	2020	Europe

NCCN esophageal and esophagogastric junction cancers	2020	USA
NCCN gastric cancer	2020	USA
*Hepatobiliary and pancreatic system****		
International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas	2012	International
European experts consensus statement on cystic tumors of the pancreas	2013	Europe
Clinical practice guidelines for the management of biliary tract cancers	2015	Japan
AGA institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts	2015	USA
EASL clinical practice guidelines on the prevention, diagnosis, and treatment of gallstones	2016	Europe
EASL clinical practice guidelines on the management of benign liver tumors	2016	Europe
Liver trauma: What current management?	2018	Morocco
International consensus guidelines for surgery and the timing of intervention in chronic pancreatitis	2019	International
NCCN pancreatic adenocarcinoma	2020	USA
NCCN clinical practice guidelines: Hepatobiliary cancers	2020	USA
Liver trauma: WSES 2020 guidelines	2020	International
*Lower gastrointestinal tract****		
Revised guidelines for the clinical management of Lynch syndrome (HNPCC): Recommendations by a group of European experts	2013	Europe
ASCRS practice parameters for the surgical treatment of ulcerative colitis	2014	USA
ECCO-ESCP consensus on surgery for Crohn's disease	2017	Europe
ASCRS clinical practice guidelines for the surgical treatment of patients with Lynch syndrome	2017	USA
JSCCR guidelines 2016 for the clinical practice of hereditary colorectal cancer (translated version)	2018	Japan
NCCN guidelines insights: Genetic/familial high-risk assessment: Colorectal	2019	USA
*Abdominal wall surgery****		
EHS guidelines on the treatment of inguinal hernia in adult patients	2009	Europe
ASCRS: Clinical practice guidelines for ostomy surgery	2015	USA
HerniaSurge Group. International guidelines for groin hernia management	2018	International

BTA British Thyroid Association, *UK* United Kingdom, *ATA* American Thyroid Association, *USA* United States of America, *CATO* Chinese Association of Thyroid Oncology, *AAES* American Association of Endocrine Surgeons, *NCCN* National Comprehensive Cancer Network, *ESMO* European Society of Medical Oncology, *ASBrS* American Society of Breast Surgeons, *AACE* American Association of Clinical Endocrinologists, *AGA* American Gastroenterological Association, *ACG* American College of Gastroenterology, *ESGE* European Society of Gastrointestinal Endoscopy, *ASMBS* The American Society for Metabolic and Bariatric Surgery Pediatric Committee, *IPMN* intraductal papillary mucinous neoplasia, *MCN* mucinous cystic neoplasm, *EASL* European Association for the Study of the Liver, *WSES*: World Society of Emergency Surgery, *ASCRS* American Society of Colon and Rectal Surgeons, *ECCO* European Crohn's and Colitis Organisation, *ESCP* European Society of Coloproctology, *EHS* European Hernia Society

place to the same issues, such as prophylactic central and lateral neck lymph node dissection, in papillary thyroid microcarcinoma [5].

In the latest version (September 2019) of National Comprehensive Cancer Network (NCCN) clinical practice guidelines in thyroid cancer, on the other hand, the recommendations and algorithm regarding prophylactic surgery were only shaped around medullary thyroid cancer [6].

The American Association of Endocrine Surgeons (AAES) published a guideline for the definitive surgical management of thyroid disease in adults in 2020. They also evaluated the previously mentioned topic and additionally gave place to prophylactic surgery in syndromic familial nonmedullary thyroid cancers, such as familial adenomatous polyposis (FAP), Cowden syndrome, Carney complex, etc. [7].

In terms of prophylactic surgery in parathyroid disorders, the sources are quite limited compared to thyroid disorders. In 2016, guidelines for definitive management of primary hyperparathyroidism of AAES prophylactic neck dissection in parathyroid carcinoma were discussed [8].

40.3 Breast

Prophylactic mastectomy was given a place in the latest version of the NCCN clinical practice guidelines in breast cancer. Eventually, the readers were referred to two discrete guidelines: 2019 Breast Cancer Risk Reduction and 2020 Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic [9]. These two guidelines comprise the identification of risk factors for breast cancer, indications for risk-reducing surgery, and the introduction of gene mutations related to breast cancer. This is a particular approach to each genetic condition, respectively [10, 11].

The American Society of Breast Surgeons (ASBrS) stated that risk-reducing mastectomy could be considered in *BRCA1*, *BRCA2*, *PTEN*, and *TP53* in their 2019 consensus guideline on genetic testing for hereditary breast cancer [12].

European Society of Medical Oncology (ESMO) published its clinical practice guidelines for cancer prevention and screening in *BRCA* mutation carriers and other breast/ovarian hereditary cancer syndromes in 2016. This guideline included recommendations on bilateral risk-reducing surgery in *BRCA1/2* mutation carriers, contralateral risk-reducing surgery in patients with previous breast cancer, and preventive surgery for specific mutations [13].

Basu et al. (2015) devised a five-step process, including history taking, calculating contralateral breast cancer risk, cooling-off period/counseling, multidisciplinary assessment, and consent using 2015 Manchester guidelines for contralateral risk-reducing mastectomy. They created a formula to calculate the lifetime risk of contralateral breast cancer and stratified breast cancer patients into different risk groups [14].

40.4 Adrenal Glands

The data about the indications of the prophylactic surgery of the adrenal glands is very limited in the literature. In the clinical practice guideline published in 2018 by endocrine society and its cosponsoring associations, place of prophylactic adrenalectomy in individuals with congenital adrenal hyperplasia was discussed [15].

European Society of Endocrinology clinical practice guideline, in collaboration with the European network for the study of adrenal tumors in 2016, recommended the surgery in asymptomatic patients (nonfunctioning) with unilateral incidental adrenal masses with radiological findings suspicious of malignancy [16]. They also suggested adrenalectomy if the lesion enlarges by more than 20% (in addition to at least a 5 mm increase in maximum diameter) during the follow-up. American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons Medical Guidelines for the Management of Adrenal Incidentalomas, on the other hand, accepted the size of the lesion as a criterion for surgery in a nonfunctioning adrenal tumor. Therefore, surgery was recommended to be considered in nonfunctioning incidentalomas ≥4 cm [17]. These approaches can also be

assessed under the concept of "prophylactic surgery," since they are performed in asymptomatic cases with no definite diagnosis of a malignant condition.

40.5 Upper Gastrointestinal Tract

The place of antireflux surgery in Barrett's esophagus has been the subject of the guidelines. American Gastroenterological Association (AGA) in 2011 recommended attempts to eliminate esophageal acid exposure for the prevention of esophageal adenocarcinoma. However, it was also stated that antireflux surgery was not more effective than medical therapy in gastroesophageal reflux disease for the prevention of cancer in Barrett's esophagus [18]. The latest NCCN guideline on esophageal cancer did not include prophylactic esophagectomy [19]. Achalasia is another benign entity of esophagus, which eventually becomes symptomatic before being diagnosed. Although the primary aim of the treatment in achalasia is symptomatic relief, treating achalasia has additional benefits, such as preventing progression to end-stage disease and carcinogenesis [20].

In 2020, Japanese gastric cancer treatment guidelines again emphasized the importance of not performing prophylactic splenectomy for advanced gastric cancer in the upper-third stomach, which does not invade the greater curvature, even for the dissection of number 10 and 11 lymph nodes [21]. On the other hand, NCCN in 2020 recommended prophylactic total gastrectomy and splenectomy in *CDH1* mutation carriers [22].

Monahan et al. (2020) indicated whether prophylactic gastrectomy was required in patients with juvenile polyposis syndrome. They could not make any recommendations regarding that since there was no adequate evidence in the literature, except a series of 42 patients, in which two had undergone prophylactic gastrectomy for benign gastric polyp burden [23].

In 2015, the eighth workshop of the international gastric cancer linkage consortium stated the vital importance of prophylactic gastrectomy in *CDH1* mutation carriers, however, could not introduce an optimal timing for the procedure [24]. American College of Gastroenterology (ACG), in the same year, pointed out the importance of identification of the borders of both esophageal and duodenal during the prophylactic gastrectomy, since a case of gastric cancer after prophylactic gastrectomy had been reported [25].

In terms of benign conditions, prophylactic coagulation of visible vessels using hemostatic forceps or endoclips immediately after the resection was offered to reduce the risk of delayed bleeding after endoscopic mucosal resection/endoscopic submucosal dissection [26].

Bariatric surgery also has several benefits, which can be accepted as preventive. American Society for Metabolic and Bariatric Surgery (ASMBS) in 2018 recommends bariatric surgery, which will lead improvement in cardiovascular and metabolic markers besides the weight loss, in adolescents with BMI $\geq$40 kg/m^2 or 140% of the 95th percentile and without comorbid diseases [27].

40.6 Hepatobiliary and Pancreatic System

Approach to asymptomatic gallstones and indications for prophylactic cholecystectomy was detailed by the European Association for the Study of the Liver (EASL) in 2016 [28]. The latest version of the NCCN clinical practice guidelines in hepatobiliary cancers accepts adenomyomatosis as a potential risk for developing gallbladder cancer [29]. 2020 NCCN guidelines on hepatobiliary cancers included prophylactic cholecystectomy in high-risk patients for gallbladder cancer and prophylactic port-site resection in gallbladder cancers [29].

The place of prophylactic gastrojejunostomy in pancreatic adenocarcinoma was mentioned in [30]. In patients who are found to have an unresectable disease during the abdominal exploration, prophylactic gastrojejunostomy was recommended if a future gastric outlet obstruction is anticipated. In terms of pancreatic cysts, AGA provided a conditional recommendation,

suggesting that patients with solid components and dilated bile duct or dubious features on endoscopic ultrasound or biopsy should undergo risk-reducing surgery [31]. Older guidelines determined cyst size ≥3 cm, thickened cyst walls, pancreatic duct 5–9 mm, nonenhancing nodule, abrupt change caliber PD with distal pancreatic atrophy, recurrent pancreatitis, rapidly increasing size, and elevated serum cancer antigen (CA) 19–9 as relative indications for surgery [32, 33].

Prophylactic surgery in chronic pancreatitis has taken place in the latest 2020 international consensus guidelines for surgery and the timing of intervention in chronic pancreatitis [34]. Patients with hereditary chronic pancreatitis were stated to have a high risk of pancreatic cancer that prophylactic resection can be considered. In addition, early surgery, which can be interpreted as a prophylactic intervention, was reported to be more beneficial in improving long-term quality of life compared to surgery in a more advanced stage of chronic pancreatitis.

In 2015, the Japanese society of hepatobiliary pancreatic surgery published the second edition of clinical practice guidelines for the management of biliary tract cancers. This guideline covered cholecystectomy and excision of the common bile duct in patients with pancreaticobiliary maljunction in terms of prophylactic surgery [35].

In terms of benign liver tumors, EASL guidelines (2016) suggested a multidisciplinary assessment for hemangiomas accompanied by Kasabach-Merritt syndrome and cases with asymptomatic focal nodular hyperplasia when the diagnosis is not firmly established with imaging in order to decide the necessity for surgical resection. Besides, surgical resection is also recommended in hepatocellular adenomas larger than 5 cm for eliminating the risk of malignant transformation [36].

40.7 Lower Gastrointestinal Tract

Monahan et al. (2020) published the latest guideline about colorectal diseases, subjected the management hereditary colorectal cancer (CRC) [23]. Colonoscopic surveillance is recommended to evaluate the adenoma burden and distribution, which can be useful for the timing of and types of prophylactic surgery in patients with FAP. Since CRC development is inevitable in these patients, total prophylactic colectomy is recommended to be planned at a time that is suitable to the patient based on the risk of cancer as assessed colonoscopically. 2019 NCCN guidelines also stated that prophylactic proctocolectomy was usually indicated for FAP in the second decade of life [37].

American Society of Colon and Rectal Surgeons (ASCRS) in 2017 recommended total prophylactic colectomy strongly in individuals with Lynch syndrome who develop colon cancer [38].

2016 guidelines for the clinical practice of hereditary colorectal cancer of Japanese Society for Cancer of the Colon and Rectum (JSCCR) recommended prophylactic colectomy/proctocolectomy in patients with FAP in their 20s [39]. However, the same guidelines did not reach a consensus on the usefulness of prophylactic colectomy in Lynch syndrome.

In 2015, ACG clinical guidelines on genetic testing and management of hereditary gastrointestinal cancer syndromes also recommended similar issues. Additionally, they highlighted the option of prophylactic colectomy in mutation carriers who have an endoscopically normal colon instead of surveillance. Indications for prophylactic surgery were stated as polyps >10 mm diameter, polyps with high-grade dysplasia, marked increases in polyp number from one exam to the next, and symptoms [25].

Prophylactic hysterectomy and bilateral oophorectomy in Lynch syndrome have been discussed in the guidelines since they are preventive for endometrial and ovarian cancer. 2019 NCCN genetic/familial high-risk assessment for CRC recommended considering prophylactic hysterectomy and bilateral salpingo-oophorectomy in patients with Lynch syndrome [37]. Vasen et al. (2013) recommended discussing prophylactic hysterectomy and bilateral oophorectomy as an option with the patients who completed fertility and had scheduled surgery for colorectal cancer [40].

In terms of inflammatory bowel diseases (IBD), there are also several guidelines subjecting prophylactic surgery. ECCO-ESCP consensus in 2017 reported to consider proctocolectomy in medically fit patients when colorectal cancer or high-grade dysplasia is detected in Crohn's colitis. Furthermore, preventive stricturoplasty was not recommended in diseased segments, which are detected intraoperatively without assessing the luminal diameter [41].

ASCRS in 2014 published practice parameters for the surgical treatment of ulcerative colitis and recommended total proctocolectomy or surveillance endoscopy for patients with UC and low-grade dysplasia [42].

40.8 Abdominal Wall Surgery

In 2018 international guidelines for groin hernia management, approach to inguinal nerves was subjected in terms of prophylactic surgery by searching the answers to the questions regarding whether the resections of ilioinguinal, iliohypogastric, and genital branch of genitofemoral nerves may contribute to reducing chronic pain incidence. No recommendations could be made since the literature is quite limited. However, pragmatic resection was stated to be a reasonable approach to an injured nerve or a nerve that interferes with mesh position. The other topic mentioned in this guideline regarding prophylactic surgery was the necessity of prophylactic mesh repair on the contralateral side in older male patients with recurrent inguinal hernia. This topic also could not get any recommendations, since there is not enough scientific evidence [43].

European Hernia Society (EHS) released its latest guidelines on parastomal hernia in 2017. The main inference of that guideline was a strong recommendation about using a prophylactic synthetic nonabsorbable mesh upon the construction of an end colostomy. However, other types of stomas did not receive such a recommendation [44]. Regarding prophylactic interventions during ostomy construction, ASCRS in 2015 also recommended the placement of lightweight polypropylene at the time of permanent ostomy construction to decrease parastomal hernia rates [45].

In 2009, EHS published its guidelines on the treatment of inguinal hernia in adult patients. In terms of prophylactic resection, only prophylactic resection of the ilioinguinal nerve for reducing the risk of chronic pain after hernia surgery was included [46].

40.9 Trauma Surgery

The latest guidelines on liver trauma were released in 2020 by the World Society of Emergency Surgery (WSES). Hepatic artery and portal vein ligations (with intact hepatic artery) were attributed as considerable choices when effective bleeding control and successful vessel repair cannot be obtained [47]. Besides, prophylactic cholecystectomy is recommended in cases, where the right or common hepatic artery is ligated to avoid gallbladder necrosis.

40.10 Minimally Invasive Interventions

Many procedures previously performed with laparotomy have been replaced by endoscopic, radiological, and ultrasonographic interventional procedures with technological advances in imaging systems. The common purpose of all these procedures is to provide maximum benefit with minimal risk and minimally invasive procedures rather than more radical procedures, as in prophylactic surgery. Nonoperative follow-up, embolization, stenting, and drainage procedures are becoming more preferred in stable solid organ injuries, such as liver and spleen [47, 48]. Endoscopic methods provide eradication of Barrett epithelium, variceal bleeding, and peptic ulcer bleeding can be stopped and prevented, cancer precursor mucosal lesions can be successfully removed, and surgery is not required [18, 49]. In fact, it can be assumed that every method that provides an easier or more minimal procedure than a more radical surgery has a prophylac-

tic purpose. These issues have taken place in several relevant approaches and will be discussed more broadly in the relevant sections.

40.10.1 Guidelines Regarding Surgical Attitudes During COVID-19 Pandemic

Prophylactic surgery for breast diseases was recommended to be deferred during the pandemic [50]. Surgery for the prophylactic indications for hereditary conditions of colorectal carcinomas was stated to be deferred 3 months [51]. Royal College of Surgeons also stated that all benign breast surgery, including risk-reducing surgery, could be deferred over 3 months during COVID-19 pandemic [52].

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41 Interventional Procedures Reducing the Needs for Conventional Surgery

Gökhan Kahraman, Özgür Özen, and Ali Harman

41.1 Introduction

As equipment quality and technology advances, interventional radiology (IR) offers clinicians a growing number of procedure options. Diagnostic (Table 41.1) and therapeutic (Table 41.2) procedures are performed in a minimally invasive fashion. Compared to conventional surgery, IR procedures guide treatment through less invasive methods. As IR procedures are minimally invasive generally, they do not require an inpatient hospital stay. Due to the lack of large incisions, procedures result in fewer side effects and shorter recovery time. Using imaging methods, such as fluoroscopy, ultrasonography, computed tomography, and magnetic resonance imaging in IR procedures provide accurate diagnosis and/or treatment. Local anesthesia is the most commonly used anesthesia method in IR procedures providing a lower incidence of anesthesia-related complications. General anesthesia is rarely required.

IR procedures are divided into two main groups: vascular and nonvascular, comprised of both diagnostic and therapeutic interventions.

The most common vascular interventional radiological procedure is diagnostic angiography. Therapeutic vascular interventional procedures include recanalization of narrowed or blocked vessels (percutaneous transluminal angioplasty (PTA), stenting, thrombolysis), or occluding vessels (embolization) to diminish tumoral/abnormal vascularization or block active hemorrhage.

Table 41.1 Diagnostic interventional radiology procedures

Biopsy Taking of sample cells or tissues for examination from a percutaneous or transvenous approach to determine the presence or extent of a disease
Cholangiography Imaging of the bile duct by x-rays and an injection of contrast medium to look for areas of blockage
Angiography Imaging of the blood vessels with the use of contrast media

Pulmonary thromboembolism caused by deep vein thrombosis can be prevented by placing retractable metallic filters in the inferior vena cava.

Chemoembolization and radioembolization are unique embolization processes tailored to cancer patients. In chemoembolization, following the selective catheterization of the feeding artery, chemotherapeutics and embolization agents are injected. In radioembolization, the same procedure is performed with the injection of agents with attached radioactive isotopes. These procedures are usually used to treat liver tumors.

Transjugular intrahepatic portosystemic shunt (TIPS) is also applied by interventional radiolo-

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Table 41.2 Therapeutic interventional radiology procedures

Ablative procedures
Chemoembolization
Radioembolization
Radiofrequency ablation
Cryoablation
Microwave ablation
Vascular
Balloon angioplasty/stent
Endovascular aneurysm repair
Embolization
Thrombolysis
IVC filters
Dialysis
TIPS (transjugular intrahepatic portosystemic shunt)
Biliary intervention
Placement of catheters in the biliary system
Placement of permanent indwelling biliary stents
Cholecystostomy
Catheter placement
Central venous catheter placement
Drainage catheter placement
Radiologically inserted gastrostomy or jejunostomy
Genitourinary
Percutaneous nephrostomy placement
Percutaneous nephroureteral stent placement
Ureteral stent exchange

gists to selected end-stage chronic liver patients to relieve portal hypertension and related conditions.

It is vital to provide vascular access when continuous or intermittent medication is required (such as chemotherapy) or when a high blood exchange volume is required (such as dialysis). Vascular access is provided by inserting a port catheter for cancer patients and hemodialysis catheters for end-stage renal disease patients. Imaging guidance not only improves the success rate, but also reduces complications of these procedures.

The second leading group of interventional radiological procedures is nonvascular procedures. The diagnostic nonvascular interventional radiological procedure is an imaging-guided biopsy. A biopsy removes tissue or fluid samples from target organs, such as the thyroid, prostate, liver, pancreas, lung, kidney, or tumors, located in other organs. Imaging methods, such as ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI), are used as guidance. A biopsy is a procedure that is carried out to reach a definitive diagnosis in many diseases. Therefore, it is of great importance in the diagnosis and future management of neoplasia-related diseases.

Therapeutic nonvascular interventional radiological procedures include tumor ablative procedures, such as radiofrequency (RF) or microwave ablation, abscess and cyst drainage, catheterization of kidney, gallbladder, bile ducts, etc.

Ablative procedures are treatments that utilize image guidance to place a needle into a target tissue such as a tumor, which will deliver the ablative effect. Electrical currents are most commonly passed through an electrode in the needle to create a region of heat that destroys tumor cells. This method is often used, especially in the treatment of liver tumors. However, it is a method that can potentially be used in many tumors.

Hereditary cancer syndromes are characterized by early-stage tumors that account for 3–20% of all cancers [1]. The management of these syndromes is carried out in a multidisciplinary fashion. IR can contribute significantly to the management of patients with hereditary cancer syndrome in diagnostic, therapeutic, and palliative procedures. The imaging methods recommended for screening of these syndromes will be discussed in the next chapter.

In the present chapter, standard interventional procedures used for managing cancer will be discussed. First, an overview of percutaneous biopsy methods will be presented, followed by therapeutic interventional procedures used as an alternative to conventional surgical methods in treating malignancies and palliative interventional procedures applied in oncology patients.

41.2 Percutaneous Biopsy

Percutaneous biopsy is a commonly used interventional procedure for obtaining tissue samples. Using medical imaging for guidance allows correct localization of the needle and targeted tumor [2–4]. Image-guided percutaneous biopsy is less invasive and less expensive than surgical methods.

The most typical indication of percutaneous biopsy is the diagnosis of malignancies, such as a primary tumor, tumor staging, metastatic disease, and posttreatment recurrence. Other indications include establishing the diffuse parenchymal disease's nature, obtaining material for microbiological analyses in suspected or known infections, and providing molecular analysis material [5–7].

Relative contraindications of percutaneous biopsy include coagulopathy, patient inability to cooperate, significant comorbidities, and pregnancy. These conditions increase the risk of complications; therefore, they should be corrected [5]. Absolute contraindications, which are rare, are as follows: lack of safe access, refusal of consent, and noncorrectable coagulopathy [7].

There are two types of needle biopsy: core-needle biopsy and fine-needle aspiration (FNA). They differ in the amount of tissue acquired. FNA provides a smaller tissue sample than core-needle biopsies.

Needle selection depends on the suspected pathology and the experience of the operator. A wide variety of needles are available for percutaneous biopsy. Needles can be classified according to diameter or gauge, length, tip configuration, and sampling mechanism [5].

Smaller-gauge needles (20–25 gauges) provide sufficient cytological material and often sufficient histological material. When multiple punctures are required, they can be used safely. They also reduce bleeding risk and complications while reaching the target lesion. It is easier to reach the lesion with larger-gauge needles (14–20 gauges). They generally provide a better sample for cytology and histology with fewer punctures—however, the risk of bleeding increases as needle diameter increases [8, 9].

Needle tips are classified as the non-cutting type used for aspiration and the cutting type used for core biopsy. Aspiration needles are the most frequently used biopsy needles. They are designed to provide samples primarily for cytologic analysis. Core biopsy needles (14–20 gauge) are larger in diameter and are used to obtain tissue samples (0.1–0.4 mm and below) for histological analysis rather than cytologic analysis [10].

Medical imaging methods, such as ultrasound, CT, and MRI, and fluoroscopy allow sampling of difficult-to-reach small lesions safely (Figs. 41.1 and 41.2) [11].

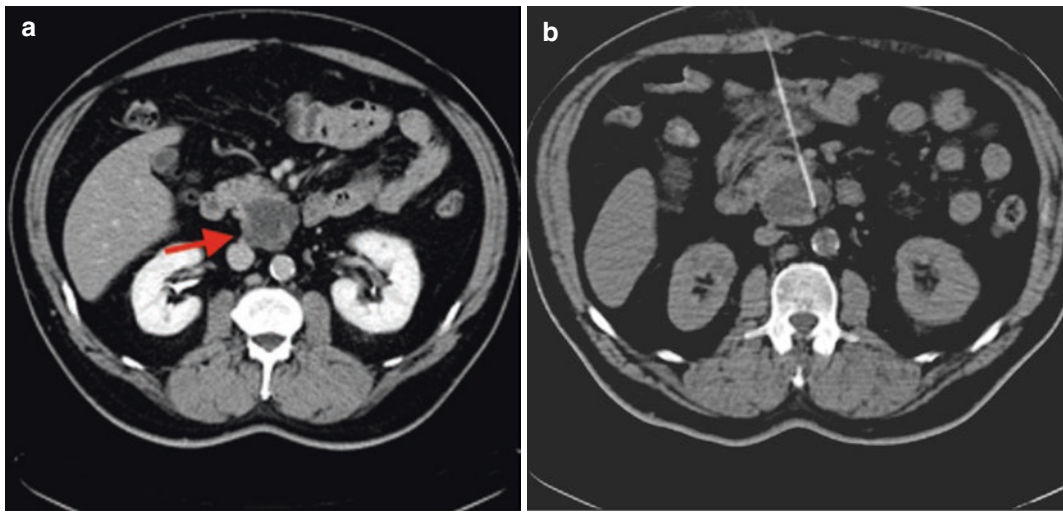

Fig. 41.1 CT-guided percutaneous FNA biopsy of the pancreatic cystic complex mass. Contrast-enhanced CT images (**a**) provide a better view of the mass's solid component (arrow). Thus, the biopsy was taken from the correct localization (**b**). FNA biopsy was reported as serous cystadenoma

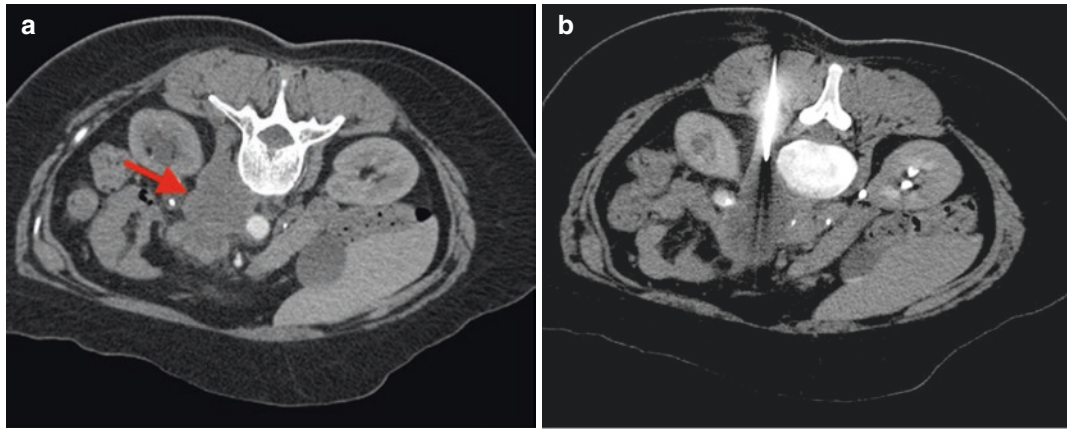

Fig. 41.2 CT-guided percutaneous core-needle biopsy of paraaortic conglomerated lymph nodes (**a**) (arrow). With the patient prone, a core-needle biopsy was performed using a posterior paravertebral approach (**b**)

41.3 Image-Guided Ablation

Image-guided tumor ablations (IGTA) induce tumor cell death. Various energy sources, including RF energy, microwave, irreversible electroporation (IRE), and cryoablation, are used for IGTA. IGTA can be used to treat many types of cancer, including lung, liver, kidney, prostate, breast, and bone cancer [12–17].

Chemical ablation is an ablative method that causes protein denaturation and cell death by injecting ethanol and acetic acid into tumor cells. US-guided percutaneous ethanol injection can be used as an alternative procedure in managing primary hyperparathyroidism caused by parathyroid adenoma and parathyroid hyperplasia in patients with increased surgical risk and patients with a previous history of neck surgery [18].

Radiofrequency ablation (RFA) is an ablative procedure designed to destroy the tumor by heating (Fig. 41.3). The conversion of radiofrequency waves into heat is the mechanism of RFA. RFA increases the local tissue temperature, which causes tumor cell death. RFA can be used to treat both primary tumors and metastases. RFA is useful in the treatment of patients with lung, liver, kidney, and bone cancers. It is feasible and safe in unresectable pancreatic cancer and cholangiocarcinoma [19, 20]. It can be used in combination with chemotherapy in the treatment of hepatocellular carcinoma. Also, RFA is an efficient alternative technique to treat osteoid osteomas. RFA provides relief to the majority of patients with painful bone metastases [21].

Microwave ablation uses energy also within the radiofrequency spectrum that causes polar molecule oscillation in tissue and heats faster than RFA. As a result, coagulation necrosis develops in tumor tissue. It is a well-established procedure for treating many benign and malignant tumors and lesions [22].

Cryoablation is a treatment that uses low temperatures to destroy tumor cells. In cryoablation, tumor tissue is frozen with temperatures reaching −20 °C, and cell deaths occur. It can treat several malignancies, including prostate, bone, kidney, and breast cancers [15, 23, 24].

IRE is an ablative procedure using nonthermal energy (electrical field) to create innumerable permanent and lethal nanopores in the cell membrane to destroy cellular homeostasis that induces apoptosis. This method does not cause necrosis as in all other ablation procedures which induce necrosis by heat or radiation. It is preferred, especially in regions where extracellular matrix, blood flow, and nerves are desired to be protected [25]. IRE can be safely performed in patients with tumors of the liver, pancreas, lung, and kidney [26–29].

Other ablative methods include high-intensity-focused ultrasound and laser ablation. High-intensity-focused ultrasound is a technique that uses ultrasonic waves to heat tissue [30, 31].

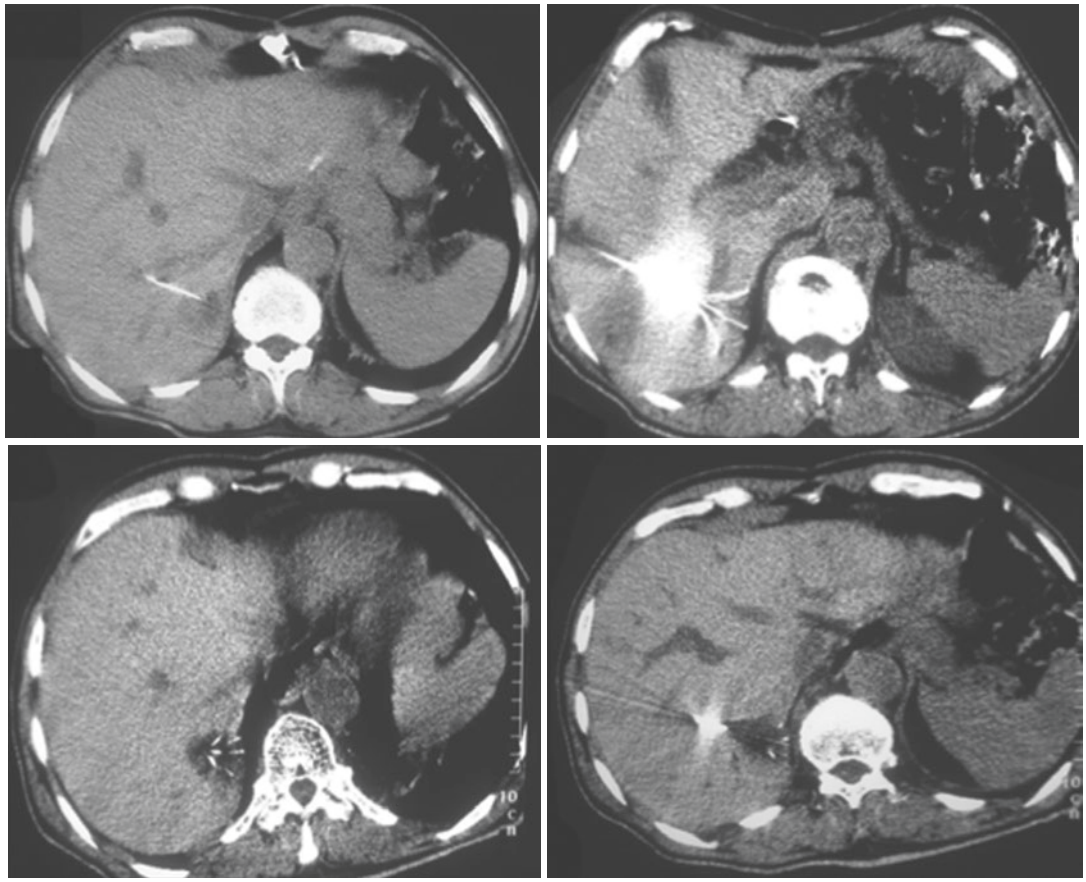

Fig. 41.3 CT-guided RFA of metastatic lesion in the right lobe of the liver

41.4 Embolization

Most chemotherapy is administered through a peripheral/central vein that circulates the whole body causing systemic effects in reaching the target tumor. With some tumors, a more targeted and higher dose of chemotherapy could be applied by selectively catheterizing the feeding artery(ies) of the tumor and injecting medication directly without the cost of systemic side effects. This method is called intra-arterial chemotherapy [32, 33].

Transarterial embolization (TAE) is a procedure in which cell death occurs by occlusion of the artery feeding the tumor with embolization materials (gelatin sponges, beads, microparticle, alcohol, glue). TAE is used to treat unresectable liver cancer, kidney cancer, and neuroendocrine tumors. It may also be used to treat uterine fibroids, aneurysms, and other conditions [33].

Transarterial chemoembolization (TACE) is a procedure in which chemotherapy and embolic agents are injected into a blood vessel feeding the tumor to occlude the tumor's blood supply and trap the chemotherapy within the tumor for enhanced potency [34]. TACE can be safely performed in patients with asymptomatic, multifocal, or large HCC without extrahepatic metastasis or vascular invasion [35]. The combined use of RF or microwave ablation plus TACE effectively treats patients with hepatocellular carcinoma (Fig. 41.4). This approach may provide better survival results than monotherapy [36].

Radioembolization is a minimally invasive procedure in which small microspheres (glass or resin) loaded with a radioactive isotope, Yttrium-90

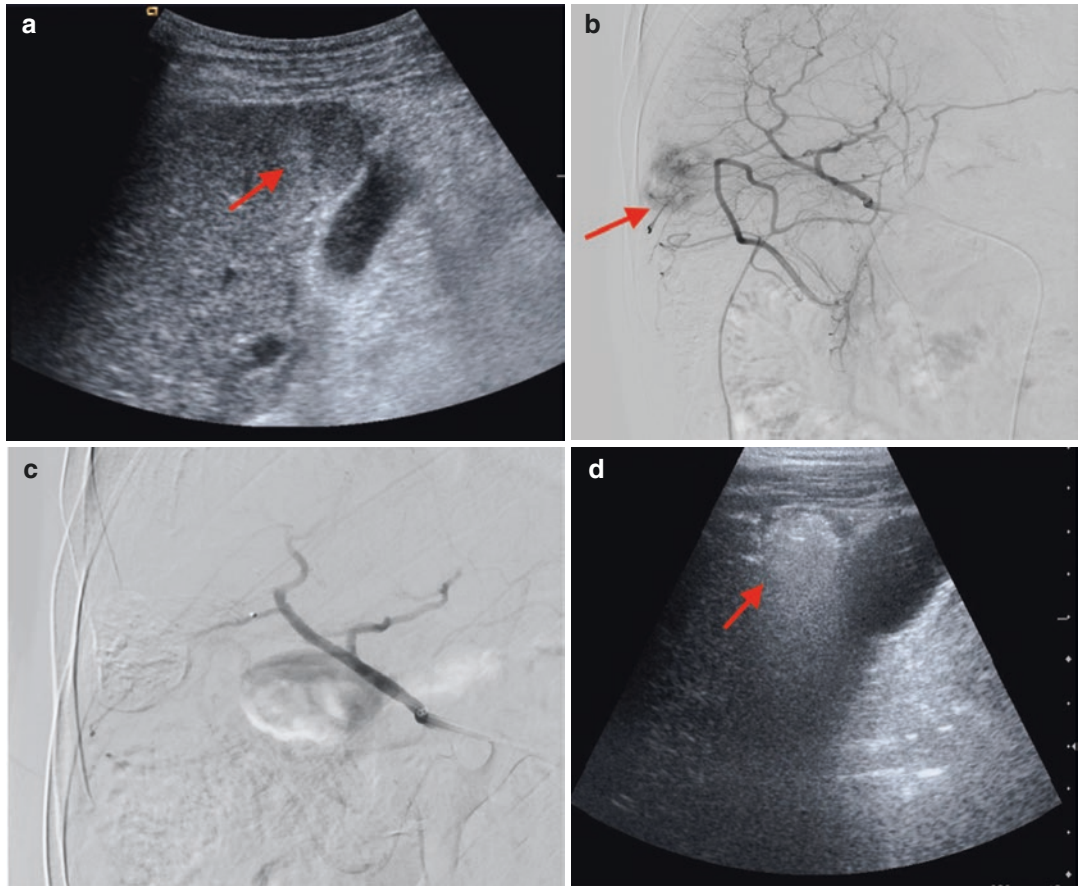

Fig. 41.4 The combination of TACE and RFA. (**a**) Ultrasonography of slightly hyperechoic liver lesion (arrow) adjacent to the gallbladder (biopsy-proven hepatocellular carcinoma). (**b**) Hypervascular liver lesion (arrow) revealed by digital subtraction angiography of the hepatic artery. (**c**) Angiography after drug-eluting beads (DEB)-TACE treatment. (**d**) Ultrasonography of the liver lesion (arrow) whose borders were chosen more clearly after DEB-TACE treatment. RFA was performed immediately after TACE in a single session

(Y-90), are injected into the vessels feeding the tumor. Radioembolization combines embolization and radiation therapy to treat cancers. High-lethal radiation dose causes cell death. Beads loaded with Y-90 occlude blood vessels feeding the tumor and deliver a high dose of radiation to the tumor while sparing the normal tissue. Radioembolization can be performed as radiation segmentectomy and radiation lobectomy. Radiation lobectomy aims to induce nondiseased lobe's growth to provide an adequate liver function to allow surgical resection [37]. Portal vein embolization (occluding the portal vein with embolization agents) also can be applied to induce hypertrophy of the nondiseased lobe [38].

41.5 Palliative Interventional Procedures

Cancer-related pain can be alleviated by interventional procedures in patients unresponsive to or unable to tolerate systemic opioids. The quality of life is improved through pain alleviation (Fig. 41.5). Interventional procedures include neuraxial analgesia (by epidural and intrathecal routes), vertebroplasty, kyphoplasty, RFA, and cryoablation for vertebral pain, sympathetic blocks for abdominal cancer-related pain (celiac plexus block and superior hypogastric plexus block), and peripheral nerve blocks

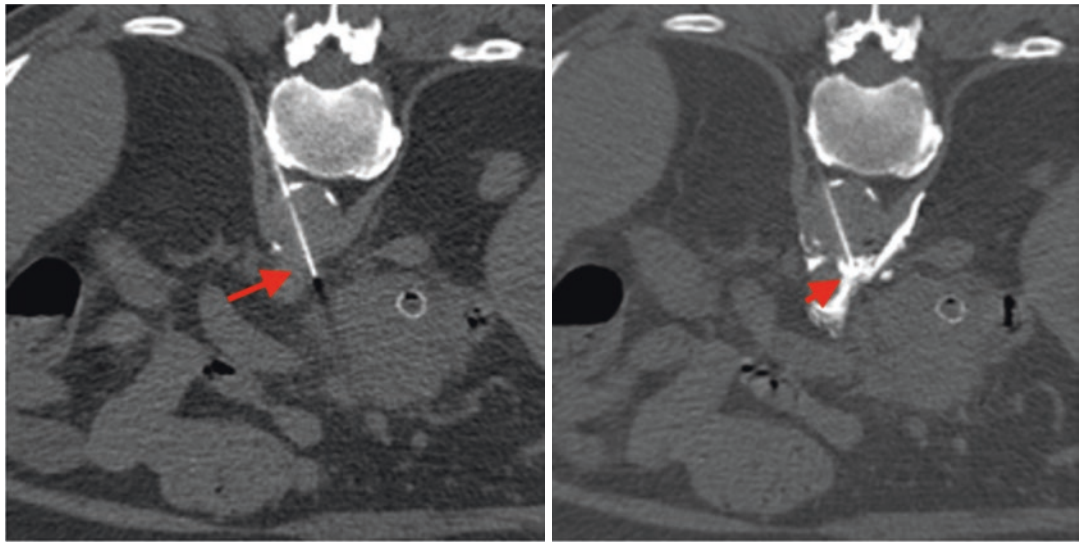

Fig. 41.5 Celiac ganglion block. The needle is passed through the aorta's anterior and posterior walls through a posterior paravertebral approach (arrow). A contrast agent injection was performed to assess the spread (short arrow) around the aorta before alcohol injection

(paravertebral blocks, blocks in the head region, plexus blocks, and intercostal blocks). Patients' symptoms can be significantly reduced by reopening the vital pathways, such as blood vessels, esophagus, and biliary tract invaded by tumors [39].

41.6 Diseases Treated with Interventional Procedures

41.6.1 Thyroid Cancer

Some studies show the clinical efficacy and safety of ablative procedures in nodule-volume reduction, improvement in symptoms, and cosmetic appearance [40]. There is not sufficient scientific evidence on its effectiveness in the treatment of thyroid carcinomas.

41.6.2 Parathyroid Adenomas

Parathyroid adenomas can be treated with ablative procedures and ethanol injection [18, 41].

41.6.3 Breast Cancer

RFA is an interventional procedure in small, solitary, localized breast cancer. However, no studies have been conducted to directly compare RFA to the current surgical resection standard [42].

41.6.4 Lung Cancer

Lung metastases and inoperable primary lung cancers can be treated with ablative methods. It is an option for selected cases that are not suitable for surgery or radiation therapy because of their general health or the tumor's size/location [43, 44].

41.6.5 Liver Cancer

TACE, radioembolization can treat primary liver tumors (hepatocellular carcinoma and cholangiocarcinoma) and liver metastasis, TACE combined with RFA, portal vein embolization, and ablative procedures [45].

41.6.6 Pancreatic Cancer

Patients with inoperable or borderline resectable, locally advanced pancreatic adenocarcinoma can be treated with IRE [46].

41.6.7 Kidney Cancer

Primary kidney cancers can be treated with ablative procedures. Treatment success is similar to partial nephrectomy [47]. The TAE method reduces the size of benign kidney tumors such as angiomyolipoma and minimizes rupture and bleeding risks [48].

41.6.8 Adrenal Gland Tumors

Treatment of hemorrhagic adrenal tumors with presurgical embolization methods provides stabilization of patients for elective surgery [49]. Embolization procedures can also reduce the tumor burden, minimize bleeding risk before surgery, and alleviate cancer-related pain [50].

41.6.9 Prostate Cancer

Transarterial chemoembolization is a new, safe, and effective procedure for inoperable prostate cancer. Prostate cancers can be treated with ablative techniques and IRE [51, 52].

41.6.10 Bone Cancer

Bone metastases (spine, pelvis, long bones) can be treated with ablative methods with or without vertebroplasty. These procedures can be curative in benign pathologies, such as osteoid osteoma, and palliative in malignant cases, such as bone metastasis pain. Embolization methods can also be used to reduce the risk of bleeding before surgery [53].

41.7 Conclusion

IO is essential in managing patients with hereditary cancer syndrome, diagnosing and treating the malignancy or related complications, and palliation. Also, it provides new treatment possibilities for patients with hereditary cancer syndrome and can be combined with conventional oncological therapies. Moreover, it can reduce the need for conventional surgery and allow physicians to provide precision cancer treatment. It has great therapeutic potential. As a result, physicians involved in the management of oncological patients should know interventional procedures.

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42 Radiological Screening for Hereditary Cancer Predisposition Syndromes

Gökhan Kahraman, Pınar Çeltikçi, and Şebnem Karasu

42.1 Introduction

Advances in cancer genetics allowed accurate diagnosis of hereditary cancer predisposition syndromes in the field of medical oncology. Hereditary cancer syndromes are characterized by early-stage tumors that account for 3–20% of all cancers, and most commonly demonstrate an autosomal dominant inheritance pattern [1, 2]. Although, they constitute a small portion of all cancers, successful diagnosis, screening, and follow-up strategies would improve morbidity and mortality rates in this group of patients. American Society of Clinical Oncology (ASCO) has published guidelines that have become the most widely used reference sources in this field, which are updated with the advances in cancer genetics [3, 4].

The diagnosis of hereditary cancer syndromes is made by detecting the underlying gene mutation following clinical suspicion. Following diagnosis, investigating other components of the syndrome is essential. Imaging plays an important role in the diagnosis, screening, and follow-up of patients with hereditary cancer syndromes. Early diagnosis would often lead to prophylactic surgery, which its importance in the management of patients with hereditary cancer syndromes is growing [5]. Therefore, clinicians should be aware of the current guidelines for the appropriate selection of radiological modality for screening, diagnosis, and follow-up, as well as screening and follow-up intervals for each hereditary cancer predisposition syndrome. Also, radiologists should be informed about the underlying genetic condition of the patient to focus on other possible sites for tumors. Although there are main guidelines in the literature, due to the infrequent nature of these conditions, the choice of imaging modality and interval is still a matter of debate for most of these syndromes. Each patient should be handled individually and should be managed in a multidisciplinary fashion.

In this chapter, radiological imaging modalities for the diagnosis, screening, and follow-up for the tumors caused by most common hereditary cancer syndromes will be discussed. First, an overview of imaging modalities will be presented, followed by a summary of most commonly encountered hereditary cancer predisposition syndromes with component tumors and specific screening/follow-up recommendations.

42.2 Imaging Modalities

Radiological imaging modalities are utilized for the screening, diagnosis, staging, evaluation of treatment response, and detection of recurrence

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after treatment of cancers in hereditary cancer predisposition syndromes.

Conventional radiography (CR), ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography/CT (PET/CT), and single-photon emission computed tomography (SPECT) are the main imaging methods used in the diagnosis and follow-up of patients with these syndromes and screening of asymptomatic mutation carriers [6, 7].

CR is an imaging technique that involves X-rays. Chest radiography and mammography are frequently used in cancer screening. This modality is usually the initial imaging method with chest and musculoskeletal systems, as it requires exposure to relatively less amount of ionizing radiation. However, projectional CR image provides limited information, and if there is accompanying clinical suspicion, further imaging is usually required.

CT is a multiplanar imaging method that provides images in three planes with excellent detail, resolution, and three-dimensional reconstructions. On the other hand, it requires exposure to larger doses of X-rays compared to CR, therefore, it should be reserved for further imaging. This is the preferred modality for the imaging of thorax, abdomen, vascular structures, and bones. CT is commonly used in oncological imaging for the detection, staging of cancers as well as in the postoperative period for recurrence follow-up.

US is a radiation-free imaging method that utilizes high-frequency sound waves. They are commonly and safely employed for screening and follow-up purposes. US is also frequently used as a guiding imaging modality for biopsies and minimally invasive treatments. US is frequently used for screening solid organs of the abdomen and superficial soft tissues, such as thyroid gland, superficial lymph nodes, breast, and testicles.

MRI is another radiation-free, multiplanar imaging method that utilizes radiofrequency waves. As it provides superior tissue contrast resolution, this modality is preferred for the imaging of the central nervous system, head and neck, breast, abdomen, and musculoskeletal system. Whole-body MRI is a popular technique in the diagnosis screening and follow-up of malignancies in patients with hereditary cancer syndrome due to high-resolution images acquired without exposure to ionizing radiation [7–10]. The basic whole-body MRI sequence is coronal short τ inversion recovery (STIR), in which the majority of lesions would appear bright (hyperintense) [9]. According to indications, axial T2-weighted, T1-weighted, diffusion-weighted, and postcontrast T1-weighted sequences can be added [11]. Many studies have reported that whole-body MRI imaging detects tumors with high sensitivity and specificity in patients with hereditary cancer syndromes [8, 12, 13].

Molecular and nuclear imaging plays an important role in assessing the extent of the disease and in posttreatment follow-up. Nuclear and molecular imaging uses radioactive substances linked to compounds used by the body's cells or compounds that attach to tumor cells. PET is an imaging method using fluorodeoxyglucose (FDG), which is a radioactive glucose molecule that accumulates in the tumor. Like PET, radioactive substances are used in SPECT. In this method, specific tumors can be detected with antibodies that bind to radioactive substances.

Although CT and PET are very useful modalities in the diagnosis and follow-up of oncological diseases, repetitive imaging increases radiation exposure and the risk of cancer development, especially in the pediatric patient group [14]. Therefore, US and MRI are the modalities that should be preferred primarily in hereditary cancer syndromes.

42.3 Hereditary Cancer Syndromes and Radiological Screening Recommendations

Syndromes of hereditary cancer predisposition with component tumors, inheritance pattern, and responsible genes are summarized in Table 42.1. Recommended radiological modalities and screening/follow-up intervals are summarized in Table 42.2, based on guidelines of the American Cancer Society (ACS), National Comprehensive Cancer Network (NCCN), and ASCO.

Table 42.1 Syndromes of inherited cancer predisposition in clinical oncology

Syndrome	Component tumors	Inheritance	Genes
Hereditary breast cancer and ovarian cancer syndrome	Breast cancer	Dominant	*BRCA1*
	Ovarian cancer		*BRCA2*
	Prostate cancer		
	Pancreatic cancer		
Li-Fraumeni syndrome	Soft tissue sarcoma	Dominant	*p53*
	Breast cancer		*CHEK2*
	Osteosarcoma		
	Leukemia		
	Brain tumors		
	Adrenocortical carcinoma		
Cowden syndrome	Breast cancer	Dominant	*PTEN*
	Thyroid cancer		
	Endometrial and other cancers		
Ataxia telangiectasia	Leukemia	Recessive	*ATM*
	Lymphoma		
Lynch syndrome	Colon cancer	Dominant	*MLH1*
	Endometrial cancer		*MSH2*
	Ovarian cancer		*MSH6*
	Renal pelvis cancers		
	Ureteral cancers		
	Pancreatic cancer		
	Stomach and small bowel cancers		
	Hepatobiliary cancers		
Familial adenomatous polyposis	Colon cancer	Dominant	*APC*
Peutz-Jeghers syndrome	Colon cancer	Dominant	*STK11*
	Small bowel cancer		
	Breast cancer		
	Ovarian cancer		
	Pancreatic cancer		

(continued)

Table 42.1 (continued)

Syndrome	Component tumors	Inheritance	Genes
Neurofibromatosis type 1	Neurofibrosarcomas	Dominant	*NF1*
	Pheochromocytomas		
	Optic gliomas		
	Meningiomas		
Neurofibromatosis type 2	Vestibular schwannomas	Dominant	*NF2*
Tuberous sclerosis	Myocardial rhabdomyoma	Dominant	*TSC1*
	Multiple bilateral renal angiomyolipomas		*TSC2*
	Ependymoma		
	Renal cancer		
	Giant cell astrocytoma		
Von Hippel-Lindau syndrome	Hemangioblastomas of retina and CNS	Dominant	*VHL*
	Renal cell cancer		
	Pheochromocytomas		
MEN1	Pancreatic islet cell tumors	Dominant	*MEN1*
	Pituitary adenomas		
	Parathyroid adenomas		
MEN2	Medullary thyroid cancers	Dominant	*RET*
	Pheochromocytoma		
	Parathyroid hyperplasia		

CNS central nervous system, *MEN* multiple endocrine neoplasia

Table 42.2 Screening recommendations for inherited cancer predisposition syndromes

Syndrome	Screening
Hereditary breast cancer and ovarian cancer syndrome	Annual MRI scans of both breasts, between ages 25 and 29 years
	Annual mammogram and breast MRI scans of both breasts, between ages 30 and 75 years
	Transvaginal ultrasound, every 6 months, beginning at age 30–35 years
Li-Fraumeni syndrome (children)	Ultrasound of abdomen and pelvis, every 3–4 months for adrenocortical carcinoma
	Annual brain MRI for brain tumor Annual whole-body MRI for soft tissue and bone sarcoma
Li-Fraumeni syndrome (adults)	Annual MRI scans of both breasts, beginning at age 20–25 years
Cowden syndrome	Annual thyroid ultrasound scan
	Annual mammogram; an annual breast MRI, beginning at age 30 years
	Annual transvaginal ultrasound, beginning at age 30 years (or from 5 years before age of earliest uterine cancer in the family)
	Kidney ultrasound scan or MRI, every 2 years, beginning at age 40 years Colonoscopy, every 5 years starting at age 35 years
Ataxia telangiectasia	Annual breast MRI in addition to an annual mammogram
Lynch syndrome	Annual pelvic ultrasound for endometrial and ovarian cancer, beginning age at 30–35 years Annual/biannual colonoscopy starting at age 20–25 years
Familial adenomatous polyposis	Annual ultrasound of the thyroid gland, beginning at age 25–30
	Annual colonoscopy starting at age 10–12 years Upper gastrointestinal endoscopy starting at age 25–30 years with an interval of 6 months to 4 years
Peutz-Jeghers syndrome	CT enterography or MR enterography, upper GI endoscopy, and colonoscopy at age 8 years; if no polyps, repeat at age 18 years; then every 3 years
	MRI with MR cholangiopancreatography of pancreas and/or endoscopic US, every 1–2 years beginning at age 30 years
	Annual pelvic examination, Papanicolaou test, and pelvic US beginning at age 25 years Annual breast MRI and/or mammography starting at age 25 years Annual testicular examination from birth to teenage years and annual testicular US starting at:
Neurofibromatosis	Annual MRI, beginning in the teenage years
Tuberous sclerosis	Ultrasound of the kidneys, every 1–3 years
	MRI or CT scan of brain and abdomen, every 1–3 years, usually until the teenage years
	Chest CT scan, if symptoms suggest a need Echocardiography, every 1–3 years from birth
Von Hippel-Lindau syndrome	Annual abdominal ultrasound, beginning in the teenage years Annual abdominal CT scan or MRI in adulthood
	MRI of the brain and spine, every 2 years beginning in the teenage years
MEN1	MRI of the brain, every 3–5 years, beginning between ages 5 and 10 years
	MRI or CT scan of the chest and abdomen, every 2–4 years, beginning at age 20 years
MEN2	MRI or CT scan of the abdomen, every 4–5 years Annual ultrasound of thyroid beginning at age 5 years or after thyroidectomy

CT computed tomography, *MRI* magnetic resonance imaging, *MEN* multiple endocrine neoplasia

42.3.1 Hereditary Breast and Ovarian Cancer Syndromes

Hereditary predisposition is seen in 5–10% of all breast cancers, and most of them are associated with genetic mutations of *BRCA1* and *BRCA2* [15] (Fig. 42.1). The cumulative cancer risk in *BRCA* mutation carriers is 72% for breast cancer and 44% for ovarian cancer in *BRCA1* and 69% for breast cancer and 17% for ovarian cancer in *BRCA2* [16]. In most series, *BRCA2*-associated breast cancers do not differ from sporadic breast cancers in terms of phenotype and behavior [17]. *BRCA1*-associated breast cancers are generally high grade, poorly differentiated, infiltrating ductal carcinomas [18]. Most *BRCA1*-associated

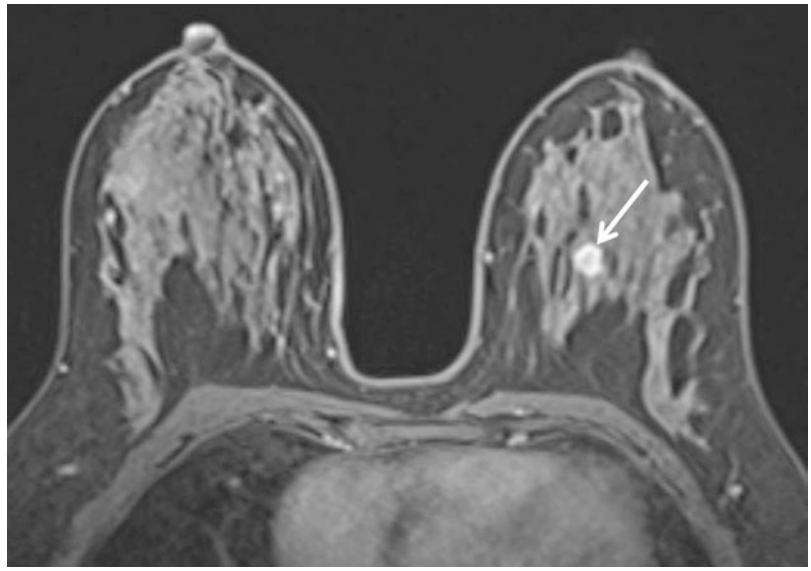

Fig. 42.1 Invasive ductal carcinoma with *BRCA1* mutation in a 38 years old woman. Her sister also had a history of breast cancer when she was 28 years old. On transverse fat-saturated T1W breast MR image, a malignant nodule, which is enhancing in the early arterial phase, is seen in the left breast (arrow)

breast cancers are triple-negative (estrogen, progesterone, and human epidermal growth factor 2 receptor-negative) [16]. Breast and ovarian cancer risk increase are more prominent in *BRCA1* carriers. Pancreatic, prostate, and other cancers risks are higher in *BRCA2* carriers [19]. Prophylactic mastectomy may be able to reduce the risk of developing breast cancer by 95% in women who carry a *BRCA1* or *BRCA2* gene mutation. Moreover, bilateral prophylactic salpingo-oophorectomy in *BRCA1* and *BRCA2* mutation carriers may reduce ovarian cancer risk by about 80% [20]. ACS and ASCO screening guidelines for individuals with *BRCA* mutations are summarized in Table 42.2 [21].

42.3.2 Li-Fraumeni Syndrome

Li-Fraumeni syndrome is an autosomal dominant disease caused by mutations in *TP53* gene and characterized by the development of multiple tumors. In one analysis, the lifetime risk of developing cancer in carriers was estimated to be 73% in men and approximately 100% in women [22]. The most common cancers in Li-Fraumeni syndrome are sarcomas, brain tumors, breast cancers, adrenocortical carcinomas, and leukemia [22]. The incidence of all sarcomas is increased, except for Ewing sarcoma. Osteosarcoma is the most common sarcoma in Li-Fraumeni syndrome.

Adrenocortical carcinoma is seen in 10–14% of *TP53* mutation carriers [23]. Moreover, the incidence of several brain tumors, including astrocytoma, medulloblastoma, ependymoma, and choroid plexus carcinoma, is increased in *TP53* mutation carriers [24]. ACS and ASCO screening guidelines for patients with *TP53* mutations are summarized in Table 42.2 [11].

42.3.3 Cowden Syndrome

Cowden syndrome is an autosomal dominant disease characterized by the development of multiple hamartomas and malignancies. It is caused by *PTEN* gene mutation. Risks of breast, colon, brain, endometrium, and thyroid malignancy are increased in Cowden syndrome [25]. Breast cancer is the most common malignancy in Cowden syndrome [26]. In addition to breast cancer, the incidence of benign breast pathologies, such as fibroadenoma, fibrocystic changes, and ductal hyperplasia, is also increased [25]. Thyroid cancers are the second most common malignancy in Cowden syndrome with papillary carcinoma being the most common type. The risk of benign pathol-

ogies, such as multinodular goiter, adenomas, and Hashimoto thyroiditis, is also increased. The incidence of papillary renal cell carcinoma, endometrial cancers, and colorectal carcinoma is increased in Cowden syndrome [27]. NCCN and ASCO screening guidelines for patients with *PTEN* mutations are summarized in Table 42.2 [28].

42.3.4 Lynch Syndrome

Hereditary colorectal cancer syndromes account for 5–10% of all colorectal cancers. Most hereditary colorectal cancer syndromes are hereditary nonpolyposis colorectal carcinoma (Lynch syndrome) and familial adenomatous polyposis (FAP). Lynch syndrome is caused by a mutation in a mismatch repair gene (*MLH1, MSH2, MSH6*) [29]. Lynch syndrome is the most common hereditary colorectal carcinoma syndrome [30]. Colorectal carcinomas occur at an early age in patients with Lynch syndrome (50% before the age of 50) and the risk of synchronous and metachronous cancers is increased [31]. In addition to colorectal carcinomas, the risks of endometrial cancer, ovarian carcinoma, small intestine and gastric adenocarcinoma, ureter and renal pelvis transitional cell carcinoma, and glioblastoma are increased [32]. Endometrial cancer is the most common extracolonic malignancy in Lynch syndrome [33]. The US Multi-society Task Force on Colorectal Cancer and ASCO screening guidelines for patients with Lynch syndrome are summarized in Table 42.2 [30].

42.3.5 Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant disease characterized by the development of multiple colorectal adenomas and caused by *APC* gene mutation [34] (Fig. 42.2). The lifetime risk of colorectal carcinoma is 100% in these patients [35]. Therefore, prophylactic proctocolectomy is essential [36]. The risks of extracolonic malignancy, such as papillary thyroid carcinoma, duodenal adenocarcinoma, brain tumors, hepatoblastoma, are also increased. Moreover, the incidence of osteoma, gastric fundic gland, and duodenal polyps and congenital hypertrophy of the retinal pigment epithelium are increased [35]. American College of Gastroenterology and ASCO guidelines for screening patients with *APC* mutations are summarized in Table 42.2 [37].

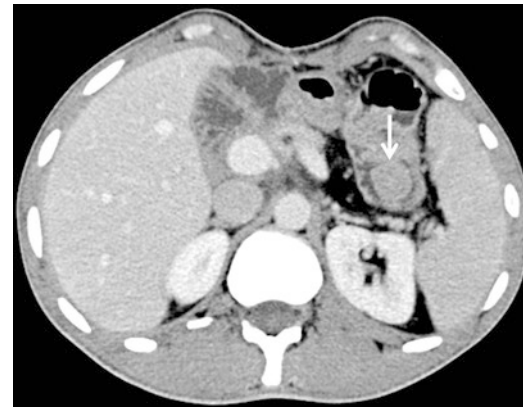

Fig. 42.2 Thirty-one years old man with familial adenomatous polyposis. He had a history of total colectomy because of numerous colonic polyps. A smooth contoured, homogenous polypoid soft tissue is seen in the jejunum lumen on transverse abdominal CT image (arrow). It was hystopathologically diagnosed as tubulovillous adenoma with high-grade dysplasia

42.3.6 Von Hippel-Lindau Disease

Von Hippel-Lindau disease (VHL) is an autosomal dominant disease characterized by the development of many malignant and benign tumors and is caused by *VHL* gene mutation [38]. Central nervous system hemangioblastoma is the most common tumor in VHL and most commonly occurs in the retina, cerebellum, and spinal cord [39] (Fig. 42.3). Endolymphatic sac tumor, clear cell renal cell carcinoma and renal cysts, pheochromocytomas, papillary cystadenoma of the epididymis, pancreatic cysts, serous cystadenoma, and neuroendocrine tumors of the pancreas are other manifestations seen in VHL [40–44] (Figs. 42.3 and 42.4). ASCO screening guidelines for patients with *VHL* mutations are summarized in Table 42.2 [45].

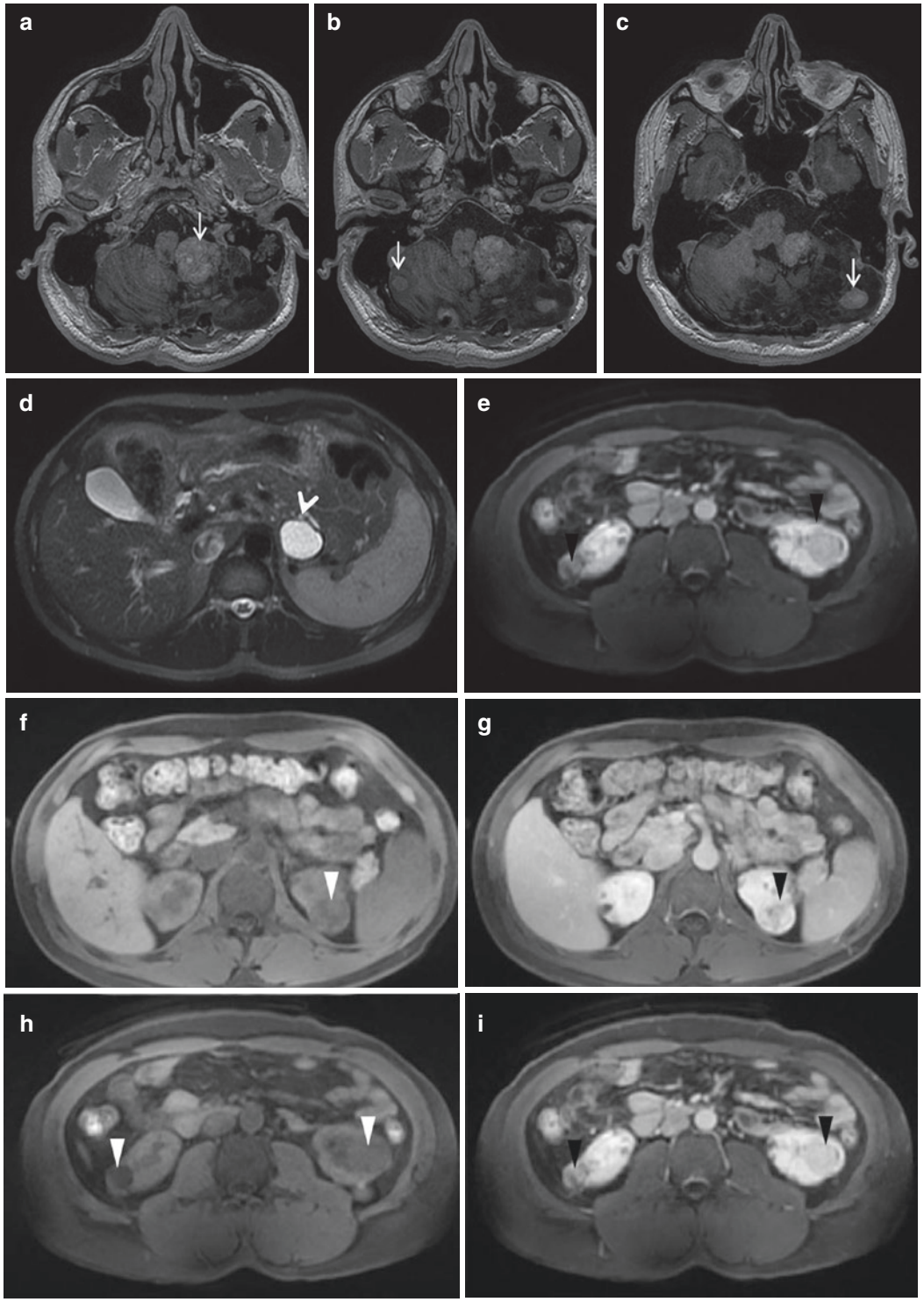

Fig. 42.3 Thirty-eight years old man with von Hippel-Lindau syndrome. (**a–c**) On fat-saturated contrast-enhanced T1W transverse MR images, bilateral enhancing cerebellar hemangioblastomas are seen (arrows). There is also a large parenchymal defect in the left cerebellar hemisphere due to previous surgical resection. (**d–e**) Transverse fat-saturated T2W (**d**) and postcontrast T1W abdomen MR images show a cystic lesion in the pancreatic tail (short arrows). (**f–i**) There are renal cell carcinomas seen in both kidneys as heterogeneously enhancing solid masses in transverse postcontrast fat-saturated T1W MR images (arrowheads)

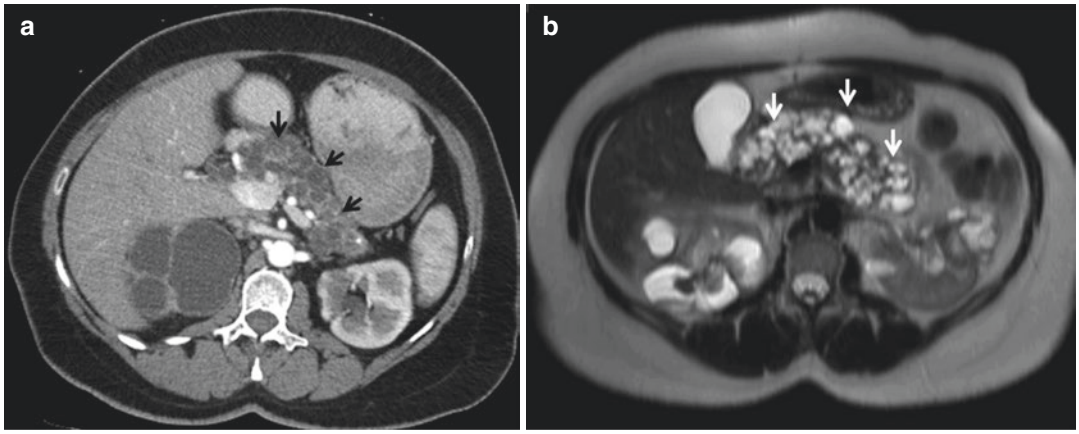

Fig. 42.4 Transverse CT (**a**) and T2W MR (**b**) images of a 38 years old woman with von Hippel-Lindau syndrome. Diffuse distribution of multiple small cysts in pancreas parenchyma (arrows)

42.3.7 Tuberous Sclerosis

Tuberous sclerosis (TSC) is a neurocutaneous syndrome characterized by the development of multiple hamartomas, benign and malignant lesions, and caused by autosomal dominant *TSC* gene mutations [46]. The most common cutaneous findings are angiofibromas and hypomelanotic macules. In the brain, cortical tubers, subependymal nodules, subependymal giant cell astrocytoma (SEGA), and dysplastic white matter lesions can be encountered [47] (Fig. 42.5). Seizures are seen in 80–90% of patients with TSC [48]. Multiple renal angiomyolipomas can be present in 80% of patients with TSC [49] (Fig. 42.5). The incidence of renal cell carcinoma is slightly increased (4%) [50]. Retinal hamartoma, pulmonary lymphangioleiomyomatosis, cardiac rhabdomyoma, sclerotic bone lesions, and hepatic angiomyolipoma are other lesions accompanying TSC [47] (Fig. 42.5). International Tuberous Sclerosis Complex Consensus Group and ASCO screening guidelines for patients with *TSC* mutations are summarized in Table 42.2 [51].

42.3.8 Multiple Endocrine Neoplasia Type 1 (MEN1)

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disease characterized by the parathyroid gland, pancreas, and pituitary gland tumors (Fig. 42.6). It is caused by *MEN1* gene mutation [52]. Primary hyperparathyroidism is the most common abnormality (90–100%). Preoperative imaging allows a more focused surgical approach. Pancreatic and duodenal neuroendocrine tumors are seen in 30–75% of MEN1 patients, and most of them are functional. Gastrinoma is the most common type, which may present with Zollinger-Ellison syndrome [53]. Pituitary tumors are seen in 30% of MEN1 patients, with prolactinoma being the most common type. Carcinoids of thymus, bronchus, stomach, duodenum, and adrenal gland are other tumors associated with MEN1. Endocrine Society and ASCO screening guidelines for patients with *MEN1* mutations are summarized in Table 42.2 [54].

42.3.9 Multiple Endocrine Neoplasia Type 2 (MEN2)

Multiple endocrine neoplasia type 2 (MEN2) is divided into three groups: MEN2A, MEN2B, and familial medullary thyroid carcinoma (MTC). MTC is the most common malignancy seen in MEN2 syndrome. MEN2A is associated with MTC, pheochromocytoma, and parathyroid tumors. MEN2B is characterized by marfanoid appearance and development of MTC, mucosal neuroma, and intestinal ganglioneuromas. The gene associated with MEN2 is *RET* [55]. In MEN2 syndrome, MTCs usually present at an earlier age

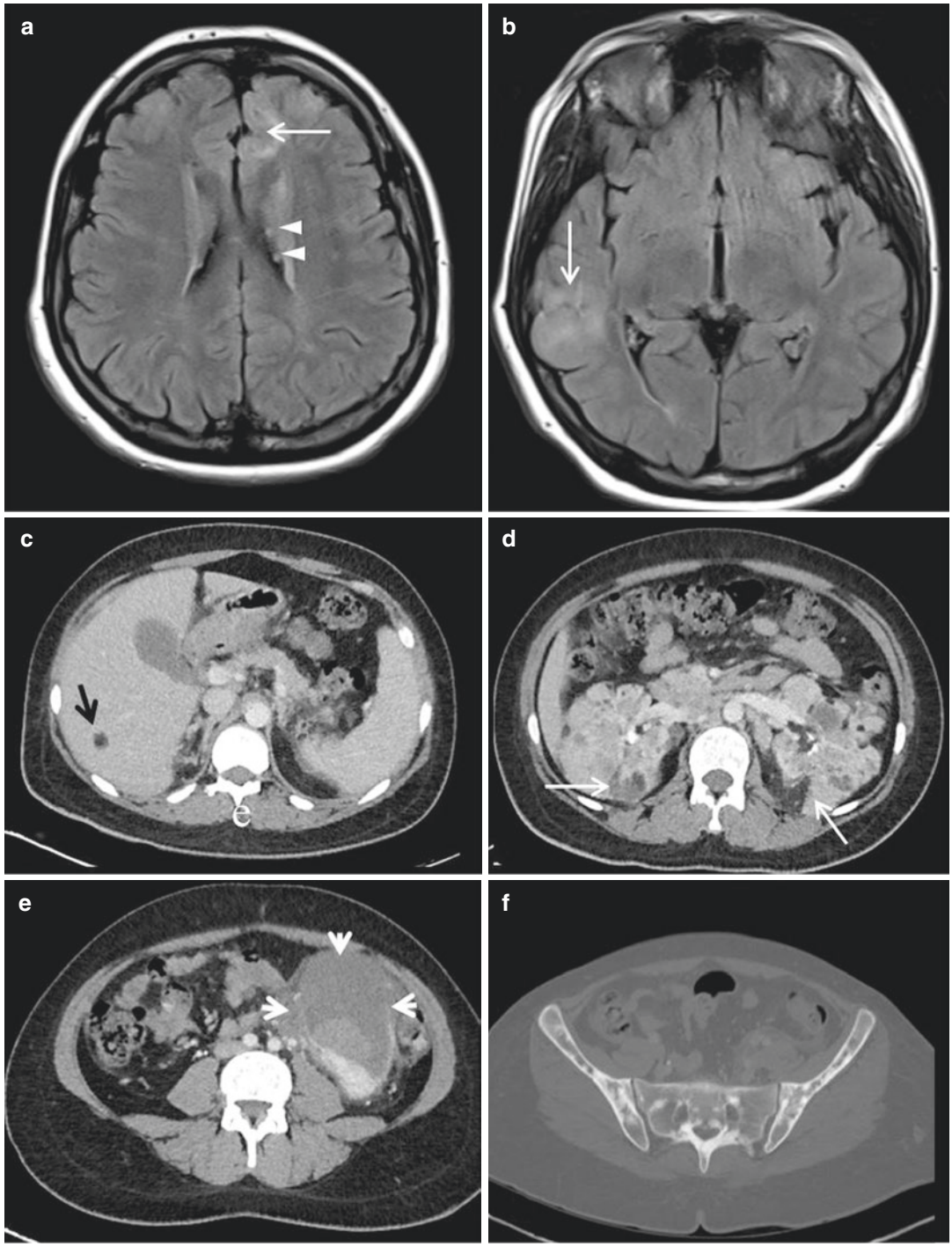

Fig. 42.5 Twenty-one years old woman with tuberous sclerosis. (**a**, **b**) Transverse FLAIR images of brain MRI show subependymal nodules (black arrows) and cortical tubers (white arrows). (**c–f**) A small hepatic angiomyolipoma (AML) is seen as a hypodense lesion in the right liver lobe (black arrow—**c**). Multiple renal AMLs in both kidneys (long white arrows—**d** and a hematoma in the left perirenal space due to an AML rupture (short white arrows—**e**). (**f**) On transverse CT images, there are multiple sclerotic hyperdense lesions seen in iliac bones

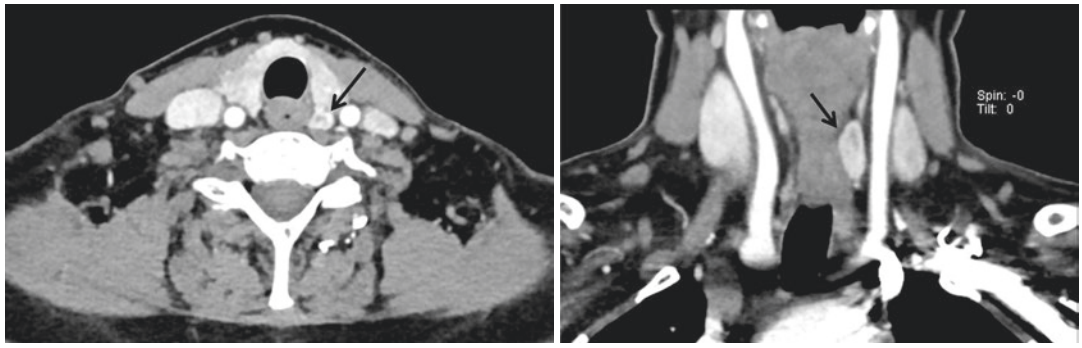

Fig. 42.6 Parathyroid adenoma in a 40 years old man patient diagnosed as MEN type 1. On transverse and coronal-reformatted CT images, a heterogeneously enhancing solid nodule (arrows) is seen in the left retrothyroid region

and in multiple numbers. Pheochromocytomas are generally bilateral. Prophylactic thyroidectomy is recommended in *RET* mutation carriers [56]. Endocrine Society and ASCO screening guidelines for patients with *RET* mutations are summarized in Table 42.2 [57].

42.3.10 Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is an autosomal dominant inherited polyposis syndrome and characterized by multiple hamartomatous intestinal, colonic and gastric polyps, and mucocutaneous melanin pigmentation (Fig. 42.7). The hyperpigmented macules are seen in the nasal and buccal mucosa, axilla, hands, feet, and genitalia. The disease is caused by mutations in tumor suppressor genes, most commonly *STK11* (70–94%) [58]. There is a lifetime risk of intestinal intussusception due to polyps. Although the polyps are not malignant, gastrointestinal tract adenocarcinomas have an increased incidence. There is also an elevated risk for breast, pancreas, ovary, uterus, cervix, testis, and lung malignancies [59]. Screening recommendations for PJS are summarized in Table 42.2 [60].

42.3.11 Neurofibromatosis Type 1 (NF1)

Neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease, is a hamartomatous neurocutaneous disorder and the most common phakomatosis. It is inherited as an autosomal dominant manner in half of the cases. De novo mutation is responsible for the disease in the other half. The *NF1* gene is located on chromosome 17q11.2 and produces neurofibromin, which has a role in tumor suppression of the Ras/MAPK pathway. Mutation of *NF1* gene causes predisposes tumor development. Pheochromocytoma, malignant peripheral nerve sheath tumor, Wilms' tumor, rhabdomyosarcoma, renal angiomyolipoma, glioma, carcinoid tumor, leiomyoma, leiomyosarcoma, ganglioglioma, and leukemia are mainly seen [61] (Fig. 42.8). The well-known diagnostic criteria of NF1 are café au lait spots, two or more neurofibromas or one plexiform neurofibroma, optic nerve glioma, osseous lesions (sphenoid wing dysplasia or thinning of bone cortex), iris hamartomas (Lisch nodules), and axillary or inguinal freckling. The neurofibroma types are localized cutaneous, diffuse subcutaneous or pathognomonically plexiform [62]. Screening recommendation for NF1 is summarized in Table 42.2 [63].

42.3.12 Neurofibromatosis Type 2 (NF2)

Neurofibromatosis type 2 (NF2) is a rare autosomal dominant neurocutaneous phakomatosis. It manifests as development of multiple tumors of central nervous system like intracranial schwannomas (mostly vestibular schwannoma), intracranial and spinal meningiomas,

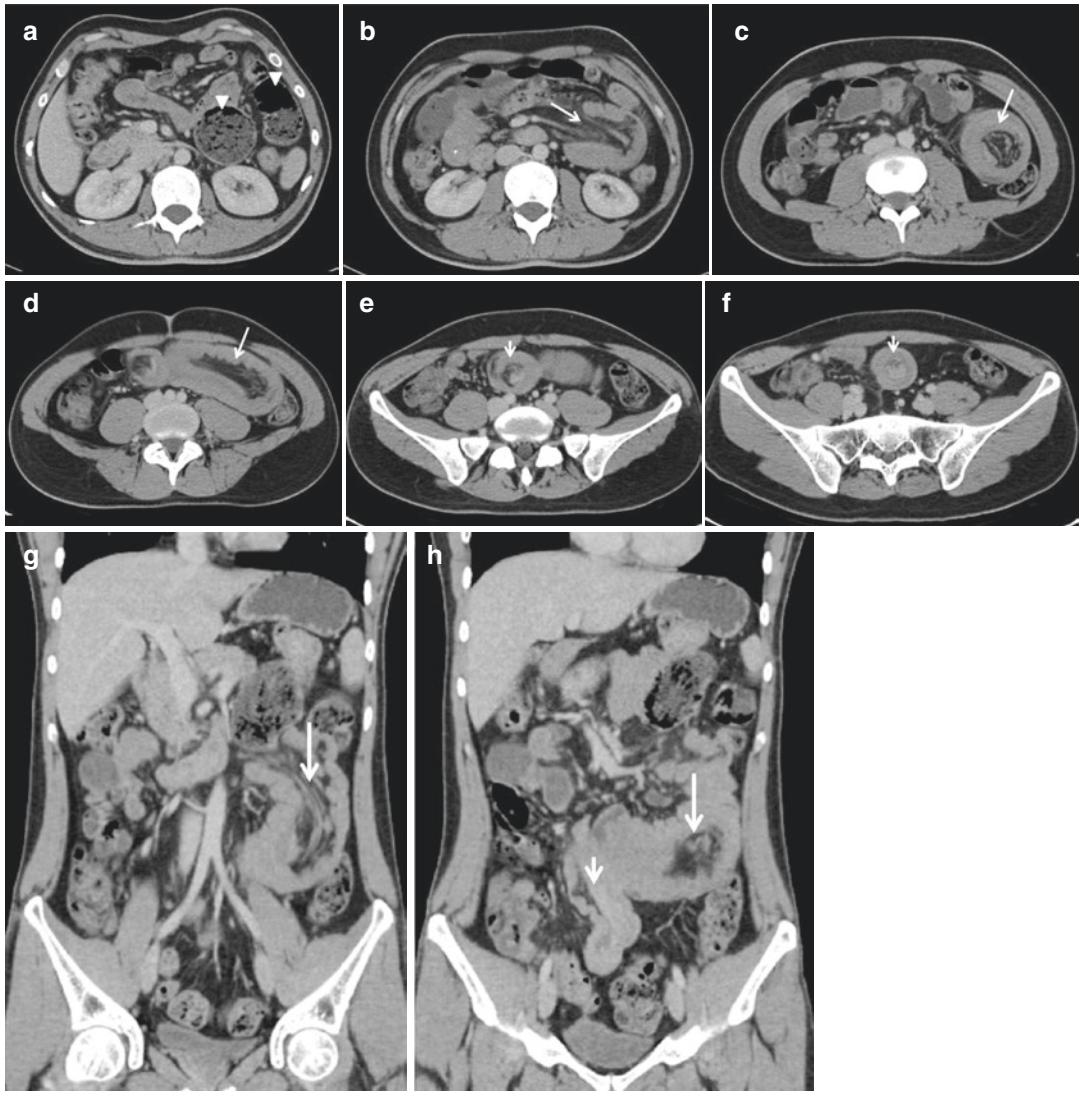

Fig. 42.7 Transverse (**a–f**) and coronal-reformatted (**g–h**) CT images of a 28 years old man with Peutz-Jeghers syndrome. Jejunal (long arrows) and ileal (short arrows) intussusceptions due to intestinal polyps. There is an obstructive dilatation and fecaloid retention in proximal jejunal segments (arrowheads)

and intraspinal-intramedullary ependymomas. It is not associated with neurofibromas [64] (Fig. 42.9). The *NF2* gene is located on the long arm of chromosome 22 (22q12), and it produces schwannomin (merlin protein), which has a tumor suppressor function and expressed in the neuronal, Schwann and meningeal cells [65]. Schwannomas are generally located in the inferior vestibular division of cranial nerve eight and tend to be multiple. Approximately 18% of solitary schwannomas occur in patients with NF2 [66]. Screening recommendation for NF1 is summarized in Table 42.2 [63].

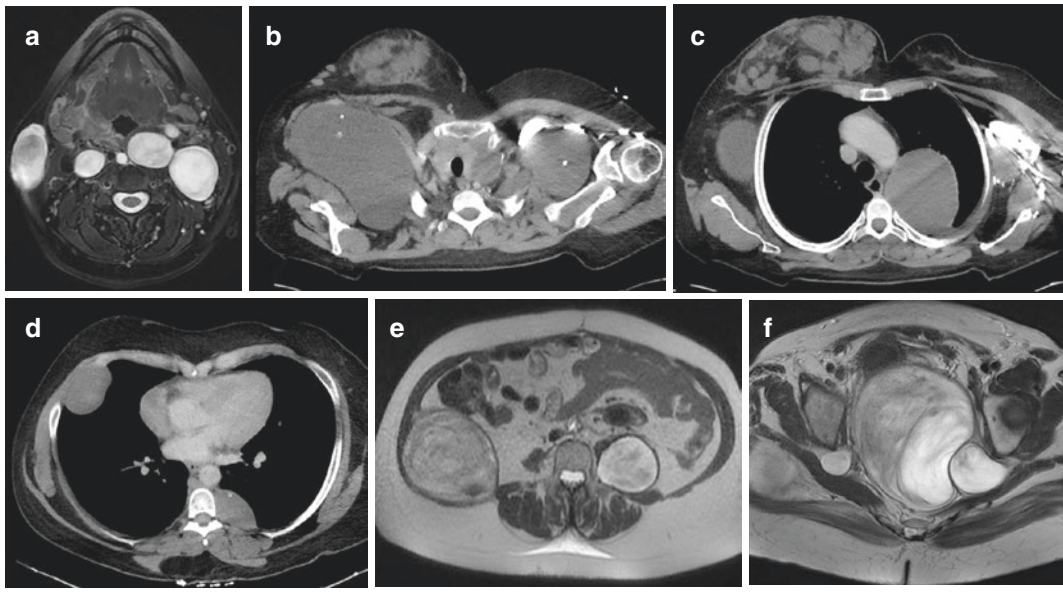

Fig. 42.8 Thirty-nine years old woman with neurofibromatosis type 1. Transverse fat-saturated T2W neck MR image (**a**), chest CT images (**b–d**), and TSE T2W abdominal MR images (**e**, **f**) show multiple soft-tissue masses extending along peripheral nerve pathways compatible with neurofibromas

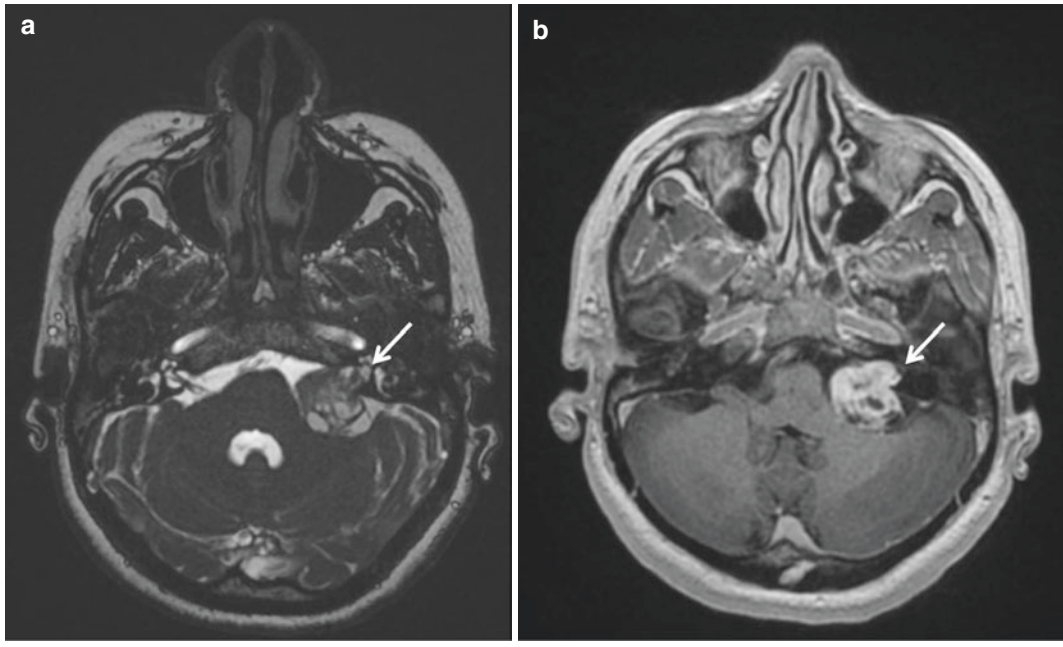

Fig. 42.9 Forty-seven years old woman with NF type 2. A vestibular schwannoma is seen on transverse gradient echo T2W (**a**) and postcontrast T1W (**b**) brain MR images as a heterogeneously enhancing mass in the left pontocerebellar angle extending to the internal acoustic channel (arrows)

42.4 Conclusion

Hereditary cancer syndromes are responsible for approximately 3–20% of all cancers. Surveillance of patients and family members with these syndromes are of great importance for maintaining early diagnosis and treatment. Imaging is essential for screening, diagnosis, and follow-up of inherited neoplasms. Early diagnosis would often lead to prophylactic surgery, which its importance in the management of patients with hereditary cancer syndromes is growing. It is important for physicians to have a thorough knowledge of screening and surveillance guidelines in hereditary cancer syndromes so as to facilitate optimal patient management.

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