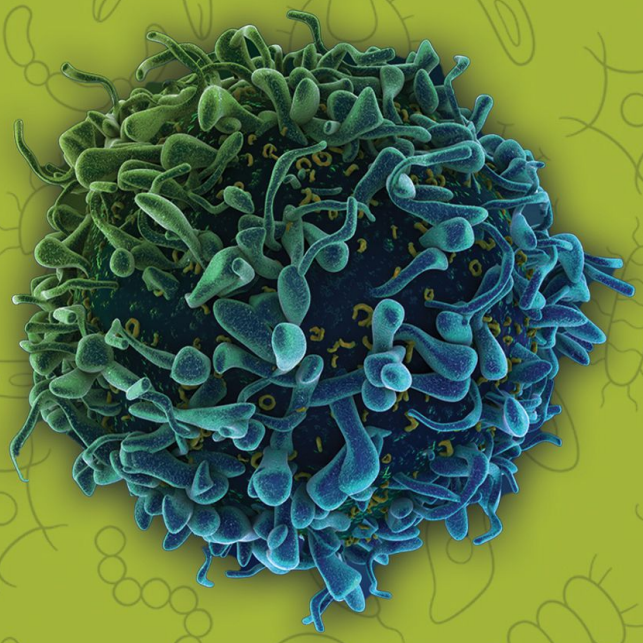
Multidisciplinary Studies in Oncology



Editors

Tuba Mert
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PRAFECE

This book, entitled Multidisciplinary Studies in Oncology, contains various oncology topics written by different authors from different disciplines in the field of oncology.

I would like to thank all my colleagues who contributed to the creation of this academic work and my esteemed Prof. Dr. Mehmet Çağlıkülekçi, whose knowledge, experience, and support I always feel both during my assistantship and expertise and in my academic life.

Asst. Prof. Tuba Mert, MD
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CONTENTS

CHAPTER I

GALLBLADDER CANCER

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1. Introduction

Gallbladder cancer (GLC) is a rare tumor with a poor prognosis and was first discovered in an autopsy by Stoll in 1877. It constitutes 2/3 of extrahepatic bile duct tumors. Gallbladder cancers characteristically grow locally invasive and generally have a low tendency to metastasize to lymph nodes. Gallbladder cancer is one of the aggressive cancers seen especially in older ages and ranks fifth among gastrointestinal cancers (1). Clinically, it frequently causes right upper quadrant pain and complaints such as weight loss and jaundice. The diagnosis of gallbladder cancer is made late because the disease clinic resembles benign gallbladder diseases. Only one third of the patients can receive a correct diagnosis in the preoperative period. Gallbladder cancers histopathologically; It is divided into four subgroups: adenocarcinoma, squamous and adenosquamous cell carcinoma, undifferentiated and rare tumors (small cell, oat cell, sarcomas). While adenocarcinoma is the most common type with a rate of 90%, squamous cell gallbladder cancers constitute 3% of all gallbladder cancers (2).

While the 5-year survival rate for stage 1 tumors, where the tumor is confined to the submucosa or mucosa of the gallbladder and does not infiltrate the serosa, is between 50-85%, this rate is 3% for stage IV cancers (3). Among the risk factors that cause the disease: Obesity, cholelithiasis, gallbladder polyps larger than 1 cm, chronic gallbladder inflammation and genetic factors (4). The only treatment method is surgical resection. Early stage 2 tumors, in which the tumor infiltrates the serosa, are associated with poor survival. In these patients, it is

necessary to perform hepatoduodenal and posterosuperior pancreaticoduodenal lymph node dissection along with resection that includes liver tissue at a depth of 2 cm of the gallbladder bed. In T3 and T4 tumors, extended liver resection as well as cholecystectomy is required for curative resection. Surgical success depends on the stage, tumor biology and completion of resection (5).

2. Epidemiology

The increasing popularity of laparoscopic cholecystectomy has led to an increase in the incidence of RHC. RHC is rare in western countries and is an important cause of mortality in countries such as Japan, India and Chile (6). This risk is much higher in white women than in black women. More than 1000 new cases of CCT are diagnosed every year in the USA, and the average age at diagnosis is 71 years (7). Although the incidence of CCTs increases with age, 70% of them are observed in women, and the male: female ratio is 2.41: 1. This rate is parallel to the incidence of gallbladder stones.

The presenting symptom is often misdiagnosed as biliary colic or chronic cholecystitis, which further delays the diagnosis. The prognosis of gallbladder cancer is poor due to the aggressive course of the tumor biology, late presentation, complexity of the anatomical position, and advanced stage at diagnosis (8). Compared with hilar cholangiocarcinoma, CCT has worse survival and shorter recurrence time. Choledochal cyst is considered a risk factor in the development of bile duct cancer.

Chronic inflammation is a major factor in carcinogenesis and is inevitably linked to malignant transformation. Therefore, with ongoing trauma leading to chronic cholecystitis, cholelithiasis may be the mechanism by which cancer develops years later. Chronic inflammation can also cause calcium deposits in the gallbladder wall. When calcium deposits increase, the gallbladder takes on a bluish tint and becomes brittle, hence the term “porcelain gallbladder.”

3. Anatomy

The gallbladder is located in the fossa vesicae biliaris, located just to the right of the lobus quadratus on the visceral surface of the liver. Its length is 7-10 cm, its width is 3 cm, and its volume is 30-60 ml. The gallbladder (SC) is adjacent to segments IV and V of the liver. Its upper surface is tightly attached to the liver by areolar connective tissue. The hepatic surface is devoid of peritoneum, which contributes to the spread of the tumor into the liver parenchyma. The main bile duct is formed by the union of the right and left

hepatic ducts. The cystic duct and the common bile duct combine to form the common bile duct. With the union of the common bile duct and pancreatic ducts, the circular muscles distal to these ducts form the Sphincter of Oddi. The gallbladder consists of fundus, corpus, infundibulum and neck regions. The tumor is located in the indibulum in 10% of the cases, and the rest is in the corpus and fundus.

Gallbladder (SC) blood supply is commonly provided from the right hepatic artery via the Cystic artery (a. cystica) (may be doubled at a rate of 12%). Venous drainage of the gallbladder is provided by many small veins. The cystic vein (v. cystica), which collects some of the venous blood, follows the cystic artery and opens into the posterior superior pancreaticoduodenal vein or portal vein. Small veins that provide venous drainage of the fundus and corpus open directly to the liver. The lymph fluid of the gallbladder, nodus cycticus, nodi foraminalis and nodi hepatici nodi coeliaci are drained (9).

4. Staging

The most widely used and up-to-date staging system in tumor staging is the TNM staging system recommended by the American Joint Commission on Cancer (AJCC) in 1998. The Japanese Society of Biliary Surgery describes the staging of gallbladder tumors; It is done according to the degree of tumor invasion (capsular, hepatic, biliary tract, etc.), whether there is lymph node metastasis and distant metastasis. Intrahepatic cholangiocarcinomas are staged similarly to hepatocellular cancer, and hilar and distal tumors are also staged together (10).

AJCC staging was renewed in 2017 and its 8th edition was published. In the 8th edition of the AJCC staging system; T category defines the depth of tumor penetration within the gallbladder wall. T1a lesions show invasion of the lamina propria, and T1b lesions show invasion into the muscle layer. For T2, the 8th edition distinguishes between peritoneal and hepatic surfaces (T2a and T2b, respectively). The tumor involved only the muscular layer of the gallbladder. T3 tumors refer to a tumor of the SC serosa that invades the liver or another adjacent organ. Ductus cysticus lymph nodes may be involved. T4 tumors are defined as tumors involving the main portal vein, hepatic artery, or 2 or more extrahepatic organs. In the 8th edition of the AJCC staging system, the N category is defined according to the number of metastatic lymph nodes (LNs) (LN; N1: 1–3 LN metastases, N2: 4 or more LN metastases) rather than their anatomical location (11).

In cases where the diagnosis of gallbladder cancer is confirmed, intraoperative determination of lymph node involvement as well as determination of T is important in choosing the surgical treatment method to be applied. Regional lymph nodes should be evaluated with a "frozen section" during surgery. Celiac, superior mesenteric and para-aortic lymph node involvement (N2) hinders R0 resection and indicates poor prognosis.

In T2 tumors (especially T2b), segment 4B-5 resection is more beneficial than wedge resection in order to eliminate occult metastases because the gallbladder veins drain into segments 4B and 5. In T3/T4 tumors, the risk of intraperitoneal spread and distant metastasis is high. If no peritoneal or nodal involvement is found, segment 4B/5 resection or right hepatectomy can be performed.

Table 1. Tumor, Node, Metastasis (TNM) classification (AJCC staging 8th edition).

T – Primary Tumor
Tx: "Primary tumor cannot be evaluated"
T0: "No signs of primary tumor"
Tis: "Carcinoma in situ; lamina propria invasion (no extension to the muscularis mucosa)"
T1: "Submucosal invasion (crossing the muscularis mucosa)"
T2: "Muscularis propria invasion"
T3: "Invasion of subserosa or non-peritonized pericolic tissue"
T4: "Direct invasion of other organs or structures and/or peritoneal perforation"
T4a: "Visceral peritoneal perforation"
T4b: "Direct invasion of other organs or tissues"
N – Regional Lymph Nodes
Nx: "Regional lymph nodes cannot be evaluated"
N0: "No regional lymph node metastasis"
N1: "1-3 regional lymph nodes positive (size of tumor in lymph nodes ≥ 0.2 mm) or all identified lymph nodes negative with the presence of any number of tumor deposits"
N1a: "Metastasis in 1 regional lymph node"
N1b: "Metastasis in 2-3 regional lymph nodes"
N1c:"Without regional lymph node metastasis; Tumor tissues or satellites in subserosa or nonperitonealized pericolic soft tissues"
N2: "Metastasis in 4 or more regional lymph nodes"
N2a: "Metastasis in 4-6 regional lymph nodes"
N2b: "Metastasis in 7 or more regional lymph nodes"

M – Distant Metastasis
M0: "No distant metastasis"
M1: "There is distant metastasis"
M1a: "Without peritoneal metastasis; Metastasis limited to 1 organ (liver, lung, ovary, extra-regional lymph nodes)"
M1b: "Without peritoneal metastasis; Metastasis in more than 1 organ"
M1c: "With or without other organ involvement; peritoneal metastasis"

5. Risk Factors

The most important risk factors for the development of gallbladder cancer include female gender, older age, cholelithiasis or other benign SC pathologies (incidental SCK is found in approximately 0.7% of laparoscopic cholecystectomies), chronic infections with Salmonella species or Helicobacter pylori, abnormal pancreatobiliary disease. duct junction, obesity, drugs (methyldopa, isoniazid, OKS?), unhealthy diet and exposure to chemicals such as nitrosamines, primary sclerosing cholangitis (annual screening of the gallbladder), porcelain gallbladder disease and SC polyps. Secondary risk factors for the development of gallbladder cancer include chronic cholecystitis, family history of cholelithiasis, high parity, smoking, exposure to chemicals such as benzene, high-carbohydrate diet and chronic diarrhea. The familial connection of SKK is unclear. Gallstones are a high risk for gallbladder cancer. Increased stone size (>3 cm) (4), increased number of stones, stone volume, and weight are associated with gallbladder cancer (12).

5.1 Gallbladder Polyps

Gallbladder polyps (SKP) are benign lesions originating from the mucosa. Nowadays, they are usually detected incidentally during examinations and scans performed with ultrasonography (USG). The majority of polyps are benign, many of which are cholesterol polyps or fibromyoglandular lesions. Although polyps are generally harmless, there is a possibility of cancer development in cases that exceed 1 cm in diameter and have adenomatous structure (13). SC polyps are seen in up to 12% of cholecystectomy specimens and 5%-7% of gallbladder ultrasonographic examinations, but only 0.7% of polyps are malignant.

Neoplastic polyps are generally larger than benign polyps. Inflammatory polyps, which are often smaller than 5 mm and multiple, are detected in preoperative examinations when they are single and larger than 1 cm; They can be confused with gallbladder cancers because they are observed as polypoid

lesions with an isoechoic structure but irregular, nodular surface in US and EUS, and in superselective cystic artery angiography, they exhibit hypervascularity by retaining contrast material similar to a tumor.

In patients with polyps, the possibility of malignancy increases in polyps larger than 1 cm, in those aged 50 and over, in cholelithiasis, solitary sessile polyps and primary sclerosing cholangitis. The American Hepato-Pancreato-Biliary Association (AHPBA) recommends removal of polyps larger than 1 cm or with avascular pedicles secondary to increased cancer incidence (45%-65% probability) (14).

Calcification of the SC wall, leading to its description as "porcelain," is associated with gallbladder carcinoma in up to 61% of patients, and cholecystectomy often must be performed in this indication.

5.2. Histopathological Features

Since the cause of gallbladder cancer is not yet clearly known, it is not possible to make definitive conclusions about its pathophysiology. The cause of the disease and possible causative factors are being investigated through experimental studies. It has been observed that gallbladder cancer develops in approximately 10% of cases with pancreatico-biliary duct junction anomaly. Choledochal cyst is considered a risk factor in the development of bile duct cancer. This observation is tried to be explained by the hypothesis that carcinogens formed by the mixture of bile and pancreatic exocrine secretion reflux into the gallbladder.

Macroscopically, CCT develops in two main forms: infiltrative and exophytic. While infiltrative cancers are observed as localized wall thickening, exophytic cancers appear as a polypoid structure protruding into the lumen and are generally observed as a mass filling the lumen. These masses, which have different macroscopic appearances, can be classified as papillary and non-papillary. The Japanese Society of Bile Duct Surgery divides gallbladder cancers into two: protruded type and flat type. In this classification, protruding type tumors can be papillary or nodular. Both protruded type and flat type cancers may show superficial or infiltrative development (14,15). Although they are most often in the fundus, they can develop in any part of the gallbladder, including the cystic duct. Multicentricity is very common, and in some cases it is even impossible to observe normal gallbladder mucosa. 90% of cases are adenocarcinoma. Other histopathological types according to their frequency: undifferentiated carcinoma, adeno-squamous carcinoma, sarcoma, carcinoid

tumor, melanoma, lymphoma and leiomyosarcoma. Very rarely, fibrous histiocytoma and myxoid tumors are also seen.

6. Diagnosis

6.1 Symptoms

Gallbladder cancers are usually asymptomatic at presentation and have vague symptoms such as nausea, vomiting, abdominal pain, aorexia, chronic inflammation, indigestion, loss of appetite and weight loss. The current symptoms of RHC often mimic those of biliary colic. Hematological and biochemical parameters do not have an important place in diagnosis. Preoperative diagnosis of gallbladder cancer can only be made with the help of imaging methods such as ultrasound, tomography and MRI. In the advanced stages of the disease, due to the development of biliary obstruction, weight loss along with jaundice, clay-colored stools, and darkening of the urine color are observed. Additionally, Mirizzi syndrome is observed in some patients. Jaundice is a relative contraindication to resection because the median disease-free survival of patients even after R0 resection is only 6 months (15). On physical examination, right upper quadrant pain, hepatomegaly, jaundice, Courvoisier's sign, palpable abdominal mass, and intestinal obstruction are findings that indicate an advanced metastatic stage. Laboratory tests show elevated bilirubin level and alkaline phosphatase. Ca 19-9, CEA and Ca 242 help in diagnosis and prognosis. At the time of diagnosis, 25% present with localization to the gallbladder wall, 35% with regional lymph node or liver invasion, and 40% with distant metastasis.

6.3 Views

Gallbladder carcinomas appear in three main forms in histological and cross-sectional imaging. These are focal or diffuse thickening of the gallbladder wall and/or irregularity in the wall, a polypoid mass arising from the gallbladder wall and extending into the lumen, and most commonly, the presence of a mass that covers the gallbladder or completely replaces it and invades the adjacent liver.

On imaging, CCT appears as a mass or wall thickening adjacent to SC polyps. The presence of calcification, smooth wall thickening and increased vascularity in the sac wall are also indicators of benign diseases such as cholecystitis or adenomyomatosis (16).

Findings supporting CCT are irregular mucosal thickening, irregular serosal thickening, or loss of differentiation between the 3 layers (17). CT

is helpful in both diagnosis and evaluation of spread and staging. With contrast-enhanced CT, it can be evaluated whether there is invasion into the liver bed, porta hepatis or a neighboring organ, and liver and lymph node metastases can be visualized. Computed tomography (CT) has a greater potential to detect portal lymphadenopathy, peritoneal implants, or vascular invasion than ultrasound; CT is the most accurate method to determine resectability, with 99% sensitivity and 76% specificity (18). MRI shows the location of the tumor in the gallbladder wall and vascular details. CCT is best revealed by T2-weighted imaging and MRCP, and appears as signal void on T1- and T2-weighted sequences. Bile ducts or liver parenchyma can be visualized with gadolinium MRI. Determining the presence of nodal disease, especially in the portahepatis, left stomach and aortocaval areas, is important for prognostic purposes and avoiding laparotomy in unresectable cases. A meta-analysis study reported that the sensitivity of PET with fludeoxyglucose F18-CT in detecting primary tumors was 93% and the specificity was 80% (19). However, the sensitivity of PET-CT in detecting occult metastases is only 56% (20). In patients with potentially resectable CCT on conventional CT, the addition of PET-CT changes the management of only 23% of patients (21).

There is no role for diagnosis by preoperative biopsy of the primary tumor that appears resectable on imaging. However, if any suspicious features in terms of resectability occur in the examinations (e.g. intrahepatic tumors, spread to vascular structures, lymphadenopathy outside the hepatoduodenal ligament or peritoneal implantations), a preoperative biopsy should be performed. Additionally, genetic tests to guide biopsy and chemotherapy may facilitate diagnosis (22).

7. Management Options

7.1 Those Previously Diagnosed with Gallbladder Cancer

Tissue biopsy is not performed before laparotomy for patients with suspected cancer diagnosis. For this reason, before radical resection, it is mandatory to take multiple core needle biopsies and send frozen sections to confirm the diagnosis of cancer (6). Although imaging methods are helpful in distinguishing benign masses, RCC can be confused with mass-forming xanthogranulomatous cholecystitis (23).

Staging laparoscopy (EL) is an important aid to identify peritoneal implants and nodal disease outside the hepatoduodenal ligament in patients with proven

or suspected Gallbladder Cancer. Spread beyond the hepatoduodenal ligament (including the celiac, retropancreatic, and aortocaval nodes) often represents metastatic disease and precludes resection. In this setting, EL is recommended for CCTs in both the NCCN guiidelines and the 2014 AHPBA (22).

Laparoscopic ultrasound (to determine local spread) further increases accuracy in identifying unresectable disease prior to laparotomy (23).

There are no randomized controlled trials comparing laparoscopic and open radical cholecystectomy for Gallbladder Cancer, but there are several single-center series reporting the safety and feasibility of the laparoscopic approach.

ERCP (Endoscopic Retrograde Cholangio Pancreatography) is another diagnostic method. In this method, which is mostly used for the diagnosis of bile duct cancer, a small tube or catheter is inserted into the bile duct through the endoscope. In the percutaneous cholangiography method, in which a thin dyed needle is inserted through the skin and under the gallbladder, imaging is performed with a medicated substance administered through the veins to check whether there is a tumor in the gallbladder. Laparoscopy, as in many diagnostic methods, is also used to detect tumors in the gallbladder and its ducts. The tumor is visualized by entering the abdominal area. PET scanning is the last method used. In this scan, it can be understood which organs the tumor has metastasized to, as well as what stage the cancer is.

7.2 Those Diagnosed with Incident Gallbladder Cancer

Although the safety and convenience of laparoscopic surgery has led to controversy in the treatment of RHC, it has led to increased applications for minimally invasive cholecystectomy. Incidental cancers are generally early stage (T1) tumors. The incidental sac tumor detection rate in all cholecystectomies is 0.19%-5.5%. The necessity of re-operation is widely accepted, as approximately half of T2 cases may have lymph node metastasis (N1). In reoperation, non-anatomical wedge resection of the liver-gallbladder bed, including 2 cm of liver tissue, and hepato-duodenal ligament and posterosuperior pancreatico-duodenal lymph node dissection should be performed. In order to achieve curative resection in T3 and T4 cases, hepatectomy including segments IV and V, or even extended right hepatectomy, should be performed (24). Incidental CCT are cancers that are not diagnosed in the preoperative period and are detected by postoperative pathological examination. CCT is not an effective treatment method other than surgical resection, and complete resection appears to be the only curative method (25).

7.3 Initial Surgery

The only treatment that offers cure for gallbladder cancer is surgery. Survival rates vary dramatically depending on whether curative resection (R0) can be achieved. The decision whether to perform resection is generally made according to the degree of tumor invasion (T) and lymph node involvement (N). The diagnosis of gallbladder cancer for the first time as a result of histopathological examination of the specimen in patients who were operated on with the preliminary diagnosis of gallstones is defined as incidental gallbladder cancer (22). Although incidental cancers are generally early stage (T), the disease can be locally advanced even if it is limited to the gallbladder wall (T2). The first lymph node to which gallbladder cancer spreads is the cystic or pericholedochal node. Most incidental diagnoses of CCT are made during pathological examination. While the cystic lymph node remains in the specimen in simple cholecystectomy, the pericholedocal lymph node is not removed. Therefore, some incidental gallbladder cancer cases are evaluated below their true stage and the necessary treatment is not applied.

Current guidelines for incidental CCT recommend re-resection for T1b, T2 and T3 tumors unless there is distant spread or poor functional status on preoperative imaging (22). The LN status of the cystic duct at the time of the initial operation is predictive of additional positive nodes in the portahepatis. Furthermore, if subsequent radical cholecystectomy reveals no residual disease, the disease-free survival of these patients is more similar to N0 than N1. Re-surgery for ISCH should provide R0 resection and locoregional LN dissection; The type of hepatic resection has proven to be less important than performing R0 resection alone (26). Studies have shown equivalent survival rates in patients undergoing hepatic wedge resection compared to formal segmentectomy or hemihepatectomy (23). Additionally, major hepatic resections are associated with worse perioperative morbidity without survival benefit (25).

Since it has been shown that lymph node metastasis (N) may occur in approximately half of T2 cases, the necessity of re-operation in these cases is widely accepted. In re-operation; Non-anatomical “wedge” resection of the liver-gallbladder bed, including 2 cm of liver tissue, and hepato-duodenal ligament and postero-superior pancreaticoduodenal lymph node dissection (extended cholecystectomy) should be performed. For early stage tumors (T1b or T2), patients should undergo radical cholecystectomy with en bloc resection of adjacent liver parenchyma and hepatoduodenal lymphadenectomy. Extrahepatic bile duct resection and reconstruction with Roux-en-Y hepaticojejunostomy are

not routinely recommended in RHC because they increase morbidity without any survival benefit. However, if the patient has a positive cystic duct border on intraoperative frozen section or direct examination, extrahepatic bile duct resection is required (15). Involvement of the common bile duct is evidence of decreased survival even after R0 resection (27).

The extent of resection in more advanced stage tumors (T3 or T4) is debated in the literature. Radical en bloc resections have been reported in patients with tumor spread to the gastro-intestinal system but without signs of distant nodal involvement (23). These operations have shown increased morbidity and mortality without any disease-free survival or overall survival benefit except in small case series. The most important determinants of long-term survival are tumor biology and stage rather than the extent of resection (28).

Lymphadenectomy is standard for T1b or more advanced tumors (29). The presence of hepatoduodenal nodal disease is not a contraindication for resection, but patients may benefit from neoadjuvant chemotherapy (29).

Portal lymphadenectomy for RHC involves the portahepatis, gastrohepatic ligament, and retroduodenal space. Tumor-associated para-aortic and celiac lymphadenopathy are generally considered metastatic disease. In a study conducted by Shirai and colleagues, the average 5-year survival was 80% in 54 patients with pathologically negative nodes, while this rate was 43% in node-positive patients (28). LN rate, as a part of positivity, has also been shown to predict postoperative survival (29). This study takes into account tumor biology (positive LNs) and extent of lymphadenectomy (total number of LNs in the sample). It has been suggested that adequate staging requires 6 LNs from the hepatoduodenal ligament (supported by LNs from more distant regions if necessary) (29).

It is suggested that in cases where the tumor has invaded beyond the gallbladder wall (T3, T4), it is necessary to perform hepatectomy including segments IVb and V, or even extended right hepatectomy, in order to achieve curative resection. While the 5-year survival rate after curative resection is reported as 50%, it is between 0.5% in cases where there is no chance of undergoing curative resection. Kondo (30) reported that radical resection was applied to 80 of 6 cases operated with the diagnosis of gallbladder cancer, extended right hepatectomy was performed in 40 of 68 Stage III and Stage IV cases, and pancreaticoduodenectomy was performed in 23 of these cases, and portal vein was removed in 23 of these cases. He also stated that resection was necessary. In this series, 3-year survival was found to be 44% in Stage III and

24% in Stage IV (M0), and it was emphasized that radical resection in these cases had a positive contribution to survival. However, the role of aggressive surgery in T3 and T4 tumors is still controversial.

8. Neoadjuvant and Adjuvant Treatment Options

The latest NCCN guidelines recommend consideration of chemotherapy or Chemoradiotherapy after resection of RHC (22). Decisions regarding adjuvant therapy should consider individual risks and benefits. There is some data suggesting that the use of adjuvant radiotherapy after R0 resection provides a survival benefit (,31).

There is no standard treatment approach for patients with unresectable and metastatic RCC. Chemotherapy is one of the treatment options. However, there is no standard approach in the chemotherapy regimens applied. In most of the studies, other tumors of the biliary tract, such as cholangiocellular carcinoma and carcinoma of the ampulla of Vater, were also included. Although they are cancers of the biliary tract, there are differences in biological behavior and different clinical courses between these cancers. Cholangiocellular cancer has a better progonosis than CCT. Fluoro-pyrimidines; 5'-fluorouracil (5-FU), 5'-fluoro2'-deoxyuridine (FUdR) and deoxyfluridine (dFUR) are the most commonly used systemic chemotherapy (CT) agents. Mitomycin C (MMC), cisplatin (CDDP) and anthracyclines; adriamycin (ADM) and epirubicin (EPI) are other chemotherapy agents used. Due to these differences, different response rates such as 0%-36% have been reported in studies conducted with 5-FU-based chemotherapy regimens (32,33).

In addition to systemic CT, there are also centers that perform local CT with selective catheterization. Giving an anticancer agent directly into the hepatic artery feeding the gallbladder ensures that the drug is found in much higher concentrations in the cancer tissue than systemic administration. Although 5-FU and MMC are the most commonly used substances for this purpose, CDDP can also be applied alone or in combination with 5-FU.

Neoadjuvant treatments have been tried in locally advanced unresectable RBCs. However, it has been stated that neither chemotherapy nor chemoradiation alone has a significant effect on survival (34,35,36). Radiotherapy can be used alone or in combination with chemotherapy for pain palliation.

The small number of cases that can undergo radical surgical treatment and the relatively high number of cases that cannot be cured after radical surgery suggest that radiotherapy (RT) can be used as adjuvant treatment in the treatment

of gallbladder cancers, as in many other organ cancers. It is suggested that intraoperative RT supported by postoperative RT will increase survival time. In cases with microscopic residual tumor localized at or near the resection margin, adjuvant RT accompanied by chemosensitization with 5-FU can be applied (36).

9. Differentiation and gene mutations

Tumor; It can be well, moderately, poorly differentiated or undifferentiated. While the prognosis is better in well-differentiated tumors, lymph node metastasis and liver invasion are observed more frequently in poorly differentiated tumors accompanied by gallstones (37). p53 gene mutation shows an increase in the level of atypia and invasion feature (38). It is suggested that there are two main morphological pathways in the development of gallbladder cancer: de novo and adenoma-carcinoma sequence. Although low-level K-ras mutation and predominant p53 alteration cause de novo cancer development, there is evidence showing that cancer development from adenoma is unrelated to p53, K-ras and APC gene mutations (39). While a correlation was observed between CD44v8-0 immunoreactivity and perineural invasion, venous spread, lymph node metastasis and poor prognosis, it was noticed that the prognosis was much better in cases with CD44v8-0 negative tumors (40).

Gallbladder cancer; It can spread by direct invasion, lymphatic, vascular, neural, intraperitoneal and intraductal routes (8). Direct invasion to the liver (segments IV and V) is observed in 50% of the cases, and invasion to the major bile ducts is observed in approximately 35% of the cases. The tumor may spread to other neighboring organs such as the pancreas, duodenum, stomach, colon, or the abdominal wall by direct invasion. By the lymphatic route, it spreads to the liver parenchyma, superior pancreatico-duodenal, posterior pancreatico-duodenal, celiac and para-aortic chain via the intramural biliary ductal plexus. Lymph flow is from the cystic lymph node to the para-aortic lymph nodes. It was observed that the tumor spread more frequently to the right hepatic duct for an unknown reason. Venous drainage of the gallbladder is generally directed towards the quadrate and caudate lobes of the liver. The tumor may spread to adjacent large vessels through vascular invasion, or it may metastasize distantly to the liver, lung, pleura or other organs (38).

10. Survival

Current treatment methods for bile duct cancer are not sufficient and new treatment approaches are needed. In order to develop new treatment methods,

it is necessary to better know the molecular biological characteristics of these cancers.

One of the most important factors in predicting survival in Gallbladder cancer disease is tumor stage. Unfortunately, in most patients, the risk of developing metastasis increases after a later diagnosis and aggressive surgical treatment.

Histological type, histological grade and vascular invasion are considered prognostic factors (38). Papillary carcinoma is the histological tumor type with the best prognosis. The prognosis is quite poor in small cell carcinomas and undifferentiated carcinomas. Lymphatic and vascular invasion indicates a poor prognosis (38). Histological grade correlates with the outcome of treatment.

Only surgery is a potentially curative treatment for gallbladder cancer. However, with this cancer, only a small number of patients have the chance for this treatment. The average life expectancy in advanced stage patients with no chance of resection is generally less than six months.

There are insufficient data to support determining the frequency or duration of follow-up imaging for CCT, but the NCCN recommends imaging every 6 months for 2 years and annually thereafter for up to 5 years (22).

The chance of surgical cure for gallbladder cancer is very low. The most important reason for this is that there are no specific symptoms that will enable early diagnosis of the disease (33). Despite aggressive surgical interventions, life expectancy is not at the desired level. However, due to the increase in laparoscopic interventions for the gallbladder, the rate of incidental early tumor detection in the sample has increased. As a result, metastases began to appear at the trocar entry sites, especially in the trocar area where the gallbladder was taken out of the abdomen. In gallbladder tumors that do not involve the serosa (exceed the mucosa), wedge resection of the liver bed is required.

In conclusion; The high survival rate and long survival in early-stage tumors show that success in improving the prognosis in gallbladder cancer, as in all organ cancers, can be achieved primarily through advances in diagnostic methods. Although the type of surgical treatment to be applied varies depending on the stage of the disease, it seems that our most effective weapon in the treatment of gallbladder cancer today is surgical treatment. Although satisfactory results have not yet been achieved, promising studies on adjuvant KT and RT are continuing. In late stage cases where resection is not possible, palliative procedures maintain their place as practices that improve the patient's quality of life, although they do not have an effect on survival.

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CHAPTER II

ONCOLOGIC EMERGENCIES

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1. Introduction

In the realm of emergency medicine, the management of oncological emergencies holds paramount importance due to their potential life-threatening nature. These emergencies can manifest as a consequence of the disease itself or arise as a complication of cancer treatment. Early recognition and prompt intervention are crucial in optimizing patient outcomes (1).

Oncological emergencies can be classified into distinct categories based on their underlying pathophysiology: metabolic, hematological, structural, and treatment-related. Each category demands a unique approach to diagnosis and management.

Metabolic emergencies arise from imbalances in biochemical processes and can include tumor lysis syndrome, hypercalcemia, and the syndrome of inappropriate antidiuretic hormone secretion. These conditions often present with a rapid onset of severe symptoms and require immediate attention.

Hematological emergencies involve life-threatening abnormalities in the blood, such as febrile neutropenia, where cancer treatment-induced low white blood cell counts render patients susceptible to severe infections. Identifying and treating these infections promptly is critical to preventing further complications.

Structural emergencies arise from the physical presence of tumors and their effects on nearby structures. Conditions like spinal cord compression and superior vena cava syndrome can lead to neurologic deficits and respiratory distress, necessitating urgent management.

In the subsequent chapters, we will delve into each oncological emergency in detail, exploring their pathophysiology, clinical presentation, and evidence-

based management strategies. Our primary objective is to empower healthcare professionals with the knowledge and skills needed to respond effectively to these critical situations.

As acutely ill cancer patients can present to any medical facility, from primary care centers to emergency departments, understanding and recognizing oncological emergencies transcend specialty boundaries. A multidisciplinary approach involving oncologists, emergency physicians, and other healthcare providers is paramount in providing timely and comprehensive care.

The dynamic interplay between the disease process and its treatment underscores the importance of vigilance in recognizing warning signs promptly. Armed with a comprehensive understanding of these emergencies, healthcare professionals can be better equipped to respond effectively and potentially save lives in the acute setting.

2. Superior Vena Cava Syndrome

The Superior Vena Cava (SVC) syndrome arises from the obstruction of blood flow within the SVC, a critical conduit for venous return to the heart (2). This obstruction commonly stems from factors like external compression by tumors, intravascular tumor invasion, or the formation of intravascular thrombi (3). Notably, thoracic malignancies, with lung cancer and lymphoma at the forefront, are the primary causes (4). The clinical presentation of SVC syndrome varies according to the degree of obstruction, ranging from subtle symptoms to acute, severe manifestations.

In cases of complete obstruction, hallmark symptoms include dyspnea (shortness of breath), facial and cervical edema (swelling), cough, chest pain, and dysphagia (difficulty swallowing) (3). Physical examination often reveals facial and cervical swelling, alongside jugular venous distention – a visible sign of increased venous pressure. Another characteristic diagnostic feature is the emergence of facial and cervical cyanosis upon elevating both arms, indicating compromised venous drainage (2).

Diagnosing SVC syndrome relies significantly on clinical assessment and the judicious application of imaging modalities. Complementary to the clinical history and physical examination, imaging plays a pivotal role in confirming the underlying etiology. Chest X-rays and contrast-enhanced thoracic Computed Tomography (CT) scans are central to visualizing the obstructing mass and assessing its characteristics. Contrast-enhanced thoracic CT scans are particularly instrumental in diagnosing SVC syndrome, illuminating intravascular thrombi and the extent of the obstructive mass (5).

The pathophysiological basis of SVC syndrome lies in the encroachment of tumors originating within or near the thoracic cavity. These tumors disrupt normal blood flow through the SVC, leading to increased venous pressure and dilation of collateral vessels. The mechanical obstruction resulting from tumor compression further exacerbates venous congestion. A profound understanding of these mechanisms is essential for accurate diagnosis and timely intervention.

Clinical manifestations of SVC syndrome span a spectrum, with severity corresponding to the extent of obstruction. Partial obstruction might herald insidious symptom progression, while complete occlusion can trigger a rapid onset of severe symptoms. Importantly, patients with pre-existing pulmonary or cardiac conditions may experience intensified symptoms due to compromised respiratory function and reduced cardiac output.

Diagnosis hinges on a comprehensive evaluation that melds clinical history, physical examination findings, and insights derived from imaging modalities. While imaging techniques are invaluable, the crux of diagnosis remains grounded in clinical acumen.

Effective management is twofold: addressing the underlying cause while concurrently alleviating acute symptoms. Interventions like stent placement and radiotherapy emerge as essential strategies, particularly in cases involving compromised upper airway patency or reduced cardiac output (6). Stents offer mechanical relief by optimizing blood flow through the SVC, whereas radiotherapy targets tumor regression, ultimately mitigating obstructive effects.

Given the intricacies of SVC syndrome, a collaborative model is imperative. A multidisciplinary team, including oncologists, interventional radiologists, and radiation oncologists, ensures comprehensive care that optimizes outcomes, manages the primary malignancy, and adeptly handles acute symptomatology. This collaborative approach guarantees a well-rounded assessment and treatment plan, tailored to individual patient needs.

3. Spinal Cord Compression in Oncology

Spinal cord compression, a significant complication of cancer, emerges when malignant cells infiltrate the vertebrae or the epidural region, resulting in the compression of the thecal sac (7). This phenomenon exerts pressure on the spinal cord and is often driven by external factors such as tumors or intravascular involvement. In response, epidural vessels experience venous congestion, leading to vasogenic edema, a hallmark of the condition (8). If not promptly diagnosed and treated, spinal cord infarction can ensue, causing irreversible neurological impairment.

The prevalence of spinal cord compression is particularly notable in malignancies originating from the prostate, breast, and lung (9). Although this condition can affect any level of the spinal cord, its most common occurrence is at the thoracic level (10). The clinical presentation of spinal cord compression shares similarities with cauda equina syndrome. Patients frequently exhibit symptoms such as heightened back pain during coughing or straining, sensory deficits, urinary retention, and anal sphincter dysfunction (9). These symptoms are often accompanied by specific clinical signs, including level-specific sensory deficits, muscular weakness, and hyperreflexia.

The cornerstone of diagnosing spinal cord compression lies in contrast-enhanced Magnetic Resonance Imaging (MRI), which provides exceptional visualization of the condition's extent and involvement (11). Once diagnosed, early intervention is crucial. The administration of dexamethasone (10 mg intravenous bolus) aims to mitigate inflammation and edema around the spinal cord, offering symptomatic relief while allowing time for further evaluation (12).

For cases demanding more intricate management, surgical decompression stands as the optimal approach (13). Neurosurgical procedures target tumor masses and pressure relief, often necessitating urgent intervention to prevent escalating neurological deficits. Complementing surgery, postoperative radiotherapy assumes a vital role, reducing the risk of tumor recurrence while potentially enhancing neurological function.

4. Tumor Lysis Syndrome

Tumor Lysis Syndrome (TLS) stands out as a pivotal oncologic emergency, arising from the rapid release of toxic intracellular substances into circulation (14). It frequently manifests during intense cytotoxic therapies designed to induce tumor cell death, particularly encountered in the course of cancer treatment. The incidence is notably higher in cancer types sensitive to chemotherapy. It is often observed during the treatment of acute lymphoblastic leukemia in both children and adults, as well as acute myeloblastic leukemia and Burkitt lymphoma in adults (14).

The underpinning mechanism of TLS revolves around the abrupt release of intracellular content, including nucleic acids and their metabolites, such as uric acid, potassium, and phosphorus, into the bloodstream (15). This phenomenon is predominantly observed after initiation of cytotoxic therapies, leading to a cascade of biochemical imbalances that have far-reaching consequences for patients' well-being (16).

Uric acid, a metabolic end product resulting from enzymatic reactions involving nucleic acids, exhibits a propensity to accumulate in the distal nephron when its levels surge within tumor cells (17). This accumulation can induce urate nephropathy, which in turn contributes to acute kidney injury and acute renal failure. Concurrently, the release of potassium and phosphorus from tumor cells into circulation can trigger clinical scenarios of hyperkalemia and hyperphosphatemia. Remarkably, the intratumoral phosphorus content often surpasses that of normal cells, accentuating the risk of significant hyperphosphatemia (18).

The intricate biochemical milieu established by TLS sets the stage for further complications. For instance, when kidneys fail to adequately excrete phosphorus, renal tubular deposition of calcium and phosphorus occurs, ultimately culminating in hypocalcemia. Timely intervention plays a pivotal role in preventing these cascading events from reaching critical thresholds.

The cornerstone of TLS management lies in proactive prevention. Particularly in patients capable of tolerating increased fluid loads, pre-chemotherapy intravenous or oral hydration assumes paramount importance. When preventative measures prove insufficient, early detection becomes pivotal. To mitigate the risk of renal failure, hydration should be optimized, and electrolyte imbalances monitored vigilantly. In cases of compromised cardiac function, meticulous electrocardiographic monitoring remains essential.

5. Febrile Neutropenia

Febrile neutropenia, a critical complication frequently encountered in individuals with documented neutropenia, is defined by the presence of a single episode of fever exceeding 38.3°C or a persistent fever above 38°C for an hour (19). Severe neutropenia itself is characterized by an absolute neutrophil count dropping below 1500/μL (20). Central to the management of patients diagnosed with febrile neutropenia in the emergency department is the early identification of the focus of infection and prompt initiation of treatment. Assessing the patient's risk can be facilitated by employing the Multinational Association for Supportive Care in Cancer (MASCC) risk scoring system (21). Notably, during physical examination, particular attention should be given to inspecting for anal abscesses.

It is noteworthy that in nearly 20% of cases, the focus of infection remains elusive (22). For patients classified as low-risk, oral therapy often proves sufficient. Numerous guidelines underscore the adequacy of amoxicillin-clavulanate in combination with ciprofloxacin administered orally for managing

febrile neutropenia in low-risk patients (23). However, for high-risk patients, an intensified approach is mandated. Hospitalization, coupled with the implementation of contact isolation, is recommended. Intravenous antibiotic therapy serves as the cornerstone of management for this cohort.

In cases where the clinical presentation is more severe, diligent monitoring, including intensive care surveillance and the incorporation of early warning systems for sepsis detection, becomes imperative. This holistic approach allows for timely intervention, optimizing patient outcomes and potentially averting the progression to sepsis-related complications.

Optimal management of febrile neutropenia necessitates a multidisciplinary approach, bringing together infectious disease specialists, oncologists, and supportive care teams. This collaborative model facilitates the seamless integration of diagnostic precision, risk assessment, and therapeutic interventions. By leveraging the collective expertise, healthcare professionals can tailor treatment strategies that effectively mitigate the potential sequelae of this condition.

6. Pericardial Effusion in Oncology

Pericardial effusion, though observed in approximately 40% of cancer cases, rarely presents with overt symptoms (24). However, if the accumulated fluid exerts pressure on the heart, it can compromise cardiac diastolic filling, resulting in hemodynamic instability and potentially leading to cardiac tamponade. This phenomenon typically evolves subacutely over days to weeks. In cases where symptomatic presentation occurs, clinical manifestations such as jugular venous distention, hypotension, and muffled heart sounds (Beck's triad) can be discerned (25).

Diagnostic confirmation is achieved through echocardiography, which provides a clear visual representation of pericardial fluid accumulation and aids in assessing its impact on cardiac function (26). Notably, electrocardiographic alterations, such as reduced voltage or electrical alternans, might manifest as well (27). Treatment strategies hinge upon the degree of hemodynamic compromise.

Conservative management can be pursued when hemodynamic parameters remain stable, although meticulous monitoring is pivotal. In cases where hemodynamic compromise is evident, therapeutic intervention is imperative. Pericardial drainage through pericardiocentesis stands as the gold standard in alleviating the hemodynamic burden posed by the effusion (28).

7. Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) in Oncology:

Frequently observed in small cell lung cancer, the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) arises as a paraneoplastic phenomenon (29). The overproduction of antidiuretic hormone (ADH) is a predominant cause of hyponatremia in cancer patients (30). Treatment modalities are contingent upon the severity of defining symptoms, tailored to the individual patient's clinical profile.

The therapeutic approach to SIADH does not deviate significantly from that employed for SIADH originating from other etiologies. Management strategies encompass fluid restriction, sodium replacement, and the application of selective vasopressin receptor antagonists (31). These measures aim to rectify the electrolyte imbalance by regulating fluid retention and sodium levels.

Navigating SIADH within the oncological context necessitates a nuanced understanding of its underpinning mechanisms and tailored management. By addressing the core physiological imbalance and adopting interventions that mitigate its impact, healthcare practitioners can contribute to improving patients' overall well-being and optimizing treatment outcomes.

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CHAPTER III

BREAST RECONSTRUCTION AFTER MASTECTOMY IN BREAST CANCER PATIENTS

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1. INTRODUCTION

According to the World Health Organization, breast cancer is the most common type of cancer among women. Breast-conserving surgery can be performed in patients with early diagnosis; however, many patients still undergo unilateral or bilateral mastectomy for treatment. In 1882, Halsted first described mastectomy as a radical operation involving en bloc resection of the skin, breast tissue, pectoralis major muscle, and axillary lymph nodes (1). Subsequently, breast reconstruction techniques aimed to eliminate chest wall deformities resulting from radical mastectomy and post-mastectomy complications. With the changes in mastectomy techniques over the years and development of breast reconstruction techniques, the current aim of breast reconstruction is to create breast tissue with a specific shape and symmetry that will correct the anatomical defect after mastectomy without affecting the oncological treatment of the patient. In addition, breast reconstruction can improve the psychological status and quality of life of patients with breast cancer. Therefore, the importance of breast reconstruction has increased, and this procedure has become an area of interest for plastic surgeons (2).

In 1895, Czerny used lipoma in the lumbar region for reconstructing a mastectomy defect, which is considered the first attempt to perform breast reconstruction (3). Subsequently, a study used intact breast tissue to reconstruct the mastectomized area in patients who underwent unilateral mastectomy. In the 19th century, local flaps were used to close skin defects after mastectomy (4). The discovery of silicone implants in 1963 was an important milestone in the field of breast reconstruction. Based on Radovan's definition of tissue expanders in 1982, researchers began performing the two-stage technique in breast reconstruction (5).

2. CANDIDATE PATIENTS FOR BREAST RECONSTRUCTION

All women who have undergone mastectomy are candidates for breast reconstruction. Therefore, it is more important to identify the group of patients for whom reconstruction cannot be performed. Patients who do not want permanent scars, those who do not have realistic expectations, those whose health status is not suitable for elective surgical procedures, and those with poor cancer prognosis and short survival expectancy constitute the group for whom breast reconstruction is not suitable (6).

3. TIMING IN BREAST RECONSTRUCTION

3.1 Simultaneous Reconstruction

Reconstruction is performed simultaneously with mastectomy. Patients diagnosed with ductal carcinoma in situ, those with stage 1 or 2 cancer, and those with low probability of receiving radiotherapy constitute the candidate patient group for simultaneous reconstruction. The advantages of simultaneous reconstruction include reduced number of operations, low cost, single-stage recovery period, shorter hospital stay, and positive mood due to unaffected self-confidence associated with body image (7). The most important disadvantage is skin necrosis and related complications that may develop as a result of circulatory problems in the mastectomy flap (8).

3.2 Simultaneous Delayed Reconstruction

Simultaneous delayed reconstruction is a two-stage reconstruction method in which a tissue expander is placed in the patient during mastectomy, which is later replaced with a permanent implant. Candidates for this method include patients with a positive lymph node biopsy result during mastectomy and those who are planned to undergo radiotherapy. The tissue expander placed during

mastectomy is inflated to preserve the natural anatomical features of the breast. The aim of this technique is to take advantage of simultaneous reconstruction without interrupting the patient's treatment by minimizing the negative effects of radiotherapy (9).

3.3 Late Reconstruction

Late reconstruction can be performed at any time after mastectomy, particularly after observing improvement in hematological effects of chemotherapy and stabilization of skin changes following radiotherapy. The major advantage of this technique is the opportunity to plan the treatment based on the changes after radiotherapy. The disadvantages include the loss of anatomical features of the breast as well as loss of the skin which are making reconstruction challenging, and increased number of operations and high costs.

4. BREAST RECONSTRUCTION METHODS

Breast reconstruction can be performed using four main methods: reconstruction with implants, reconstruction with autologous tissues, reconstruction based on the combined use of autologous tissues and implants, and reconstruction via fat injection.

4.1 Reconstruction with Implants

Currently, reconstruction with implants is the most commonly used reconstruction method (10). Patients with a low body mass index, those who do not want to undergo multiple surgeries, those with small or medium breast volumes without ptosis constitute the most suitable patient group for this method. Although this method is not suitable for patients with large breast volume and ptosis, cosmetically ideal results can be achieved in this patient group via implant placement and simultaneous reduction of the breast skin, which can make it suitable for the implant.

There are two types of implants: permanent implants and tissue expanders. Permanent implants consist of an outer silicone sheath and inner silicone gel, whose volume cannot be changed. There are two different types of tissue expanders, with a common silicone outer sheath. Some expanders have a reservoir that can only be filled with saline, whereas the other expander type is prefilled with a certain proportion of silicone gel, and the remaining part can be filled with saline. The implant can be inflated using a port connected to the tissue expander implant.

4.1.1 Single-Stage Reconstruction with Permanent Implants

This method can be applied in patients with good blood supply to the skin after mastectomy, those with adequate pectoral and serratus anterior muscle integrity to cover the prosthesis, and those with low probability of undergoing radiotherapy. The implant is placed under the pectoral muscle. As the pectoral muscle is inadequate to cover the lateral part of the implant, it is covered with the serratus anterior fascia.

4.1.2 Single-Stage Reconstruction with Tissue Expander Implants

Cases in which the skin blood supply remains uncertain after mastectomy and the pectoral and serratus anterior muscles are inadequate to cover the prosthesis, a tissue expander implant is placed in the subpectoral plane and inflated to a volume that will not disrupt skin circulation. This is performed to prevent further disruption of skin circulation using a permanent implant. Under this category, the most popular implant is Becker prostheses. Becker prosthesis was first used by Becker in 1984 (11). This prosthesis consists of two separate lumens intertwined with each other. The outer lumen is filled with silicone gel, and the volume of the outer lumen is constant. The inner lumen is empty and can be inflated with saline by the surgeon during or after surgery until the desired volume is reached. There are different types of Becker prostheses in which the volume of the silicone gel is 25%–50% of the total prosthesis volume.

After the completion of postoperative wound healing, the implant is inflated at regular intervals in an outpatient setting until the desired volume is reached. When the desired volume is reached, the external port connected to the tissue expander that allows unilateral fluid flow is removed via a small incision under local anesthesia, and the reconstruction is completed. Currently, implants in which the port is integrated into the tissue expander have also been developed. In tissue expanders with integrated ports, reconstruction can be completed when the desired volume is reached without requiring a second intervention to remove the port.

4.1.3 Two-Stage Reconstruction with Tissue Expander Implants

Indications for two-stage reconstruction with a tissue expander implant are the same as single-stage reconstruction with a tissue expander implant. When applied simultaneously, the aim of this method is to protect the skin from the negative effects of radiotherapy. The purpose of using this method in the late

period is to expand the inadequate skin using a tissue expander implant. In the second session, the tissue expander is replaced with a permanent implant.

4.2 Reconstruction based on the Combined Use of Autologous Tissue and Implants

When the volume of the autologous tissue to be used in breast reconstruction is inadequate, the volume deficiency is compensated by the use of implants. The most popular example is the use of a latissimus dorsi muscle–skin flap with an implant. After the latissimus dorsi flap is passed from the axillary region to the breast region through the prepared tunnel the reconstruction is completed by placing an implant under the flap to obtain the desired volume.

4.3 Reconstruction with Autologous Tissues

Although reconstruction with autologous tissues has the ability to create a more natural breast tissue than reconstruction with implants and is associated with high patient satisfaction, its frequency has decreased in recent years (12,13). The major factors responsible for this decrease include the need for microsurgical experience, long operation times, and high hospital costs. In reconstruction with autologous tissues, the prepared flap can be transferred to the mastectomy site as a pedicled flap with its original blood supply intact. Alternatively, it can be prepared in a distant area and transferred to the mastectomy site as a free flap using microsurgical methods.

4.3.1 Pedicled Flaps Used in Autologous Reconstruction

Transverse Rectus Abdominis Myocutaneous (TRAM) Flap: The skin, subcutaneous tissue, rectus fascia and muscle, and epigastric artery and vein are harvasted in a pedicled manner and transferred to the mastectomy site by passing through the subcutaneous tunnel. Here, the flap is shaped to form the breast tissue. It is a preferred method in patients with sufficient tissue in the abdominal region, especially in patients with a body mass index of <30. It is contraindicated in patients with previous abdominal surgery and obesity. However, in the postoperative period, there is a risk of laxity, weakness, and hernia development in the abdominal region (14).

Latissimus Dorsi Flap: The thoracodorsal artery and vein can be used as a pedicled, muscle-only, or muscle–skin flap. It is transferred from the axillary region to the mastectomy site. It must be used together with the implant to achieve the desired result. It acts as a salvage flap in cases of implant reconstruction with complications or failed autologous reconstructions.

4.3.2 Free Flaps Used in Autologous Reconstruction

TRAM Flap: The skin, rectus fascia, and part of the muscle in the abdominal region are harvasted in a pedicled manner with the deep inferior epigastric artery–vein. At the mastectomy site, internal mammary or thoracodorsal vessels can be used as a recipient vessel for anastamosis.

Deep Inferior Epigastric Artery Perforator Flap (DIEP): This flap has the same skin and subcutaneous tissue as the **TRAM** flap, but the rectus fascia and muscle are not included. One or two vessels supplying blood to the skin (perforating vessels) are dissected down to the deep inferior epigastric pedicle. As the rectus muscle and fascia are preserved, deformities such as abdominal hernia and weakness, which can be observed after TRAM reconstruction, are observed less frequently (15).

Superficial Inferior Epigastric Artery Perforator Flap: This flap contains the same abdominal tissue as the **DIEP** flap, but the feeding pedicle in this flap is the superficial inferior epigastric artery. The major disadvantages are that it is technically difficult to prepare, and reconstruction can only be performed in 30% of the population (16).

Superior Gluteal Artery Perforator (SGAP) Flap: This is a perforator flap involving the skin and subcutaneous tissue in the upper part of the gluteal region. It is useful in patients with inadequate abdominal tissue. The advantage is that the donor area scar can be easily concealed through underwear. The disadvantages are that it is technically difficult to prepare and the sciatic nerve can be damaged.

Inferior Gluteal Artery Perforator Flap: This is a perforator flap involving the skin and subcutaneous tissue in the lower part of the gluteal region. The associated indications for use, advantages, and disadvantages are the same as those for SGAP flap.

Other Free Flaps: The transverse gracilis perforator flap involves the skin subcutaneous tissue of the medial thigh over the gracilis muscle, which is nourished by medial circumflex femoral vessels. The thoracodorsal artery perforator flap contains the same skin subcutaneous tissue as the latissimus dorsi flap, but it is nourished by thoracodorsal vessels.

4.4 Reconstruction via Autologous Fat Injection

Fat injection is often used as a complement to reconstruction with implants to achieve better cosmetic results. As adipose tissue is metabolically active, there is a debate that cytokines, hormones, or growth factors

secreted from the injected adipose tissue can increase the oncologic risk and cause cancer recurrence. Clinical studies have shown that fat injection does not increase the oncologic risk (17,19). Furthermore, although it is believed that calcifications observed in the injected fat can make mammographic follow-up difficult, clinical studies have shown that calcifications observed after fat injection are different from those associated with cancer and that an experienced radiologist will not have difficulty in differentiating them (20,21). During partial breast defect reconstruction, the fat obtained from the patient's body is centrifuged and then injected into the defect area with special cannulas. During total breast reconstruction after total mastectomy, special bras that create negative pressure with vacuum are used and expand the skin in the mastectomy area and a realistic breast image can be obtained via fat injection under the expanded skin in intermittent sessions (22).Complications that may be observed after fat injection include cyst formation, fat necrosis, microcalcification, infection, palpable nodule formation, and contour irregularities with incidences ranging from 1% to 7% (23,24).

5. NIPPLE–AREOLA RECONSTRUCTION

There are many methods for nipple and areola reconstruction. The most popular nipple reconstruction methods are C-V flap, Star flap, and Skate flap, all of which are based on the reconstruction of the nipple using transposition flaps, with a local random feeding pattern. In women with a large contralateral nipple, part of this nipple can be used for reconstruction. Filling materials or costal cartilage can be used to provide nipple projection (25, 26).

Creation of a new areola by tattooing is a frequently used method in areola reconstruction (27). Further, full-thickness skin grafts from the contralateral breast areola, medial thigh, or labial region may be used less frequently.

6. APPLICATIONS FOR THE CONTRALATERAL BREAST

One of the most important issues after mastectomy is to ensure the aesthetic harmony of the reconstructed and contralateral breasts. Procedures related to breast symmetry can be performed simultaneously with or after the reconstruction. To achieve symmetry, augmentation of the contralateral breast in women with small breast volume and reduction of the contralateral breast in women with large breast volume are appropriate options. Mastopexy and augmentation surgery can be performed to achieve symmetry in patients with ptotic breasts.

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CHAPTER IV

LOW-GRADE GLIOMAS

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1. Low-Grade Gliomas

1.1 Classification and Epidemiology

Gliomas are the most common primary brain tumors in adults, with an incidence rate of 6.5 per 100,000 in the US. Low-grade gliomas (LGGs) are classified as WHO grade I and 2 tumors, including astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas (1-3). Here, we focus on WHO grade 2 gliomas. LGGs have better prognoses than anaplastic types; the 10-year survival rate for grade 2 astrocytomas is 35%. These tumors can transform into high-grade forms, with 50% to 75% of grade 2 gliomas changing within 6 to 7 years. LGGs aren't localized to specific brain areas but are common in frontal (44%), temporal (28%), and parietal (14%) lobes (1). Interestingly, cerebellar LGGs have a better prognosis than supratentorial ones (4). Diagnosis is typically at 39.4 years, varying by race (40 Caucasian, 34 African American) but not sex. Factors linked to longer survival include younger age, Caucasian race, tumor histology, and extent of removal (4, 5). The most common histologic LGG type is astrocytoma (69.3%), followed by oligodendroglioma (21.1%) and mixed glioma (9.6%). Risk factors for gliomas involve high-dose radiation, aging, and hereditary disorders like Li-Fraumeni syndrome and neurofibromatosis type 1 (5).

1.2 Clinical Presentation and Symptom Management

The primary initial symptom of LGGs is seizures (65%-95%), followed by headaches (40%). Tumor mass effect symptoms are less common due to slow

growth (average 4.1 mm/yr).(6) Levetiracetam is the preferred antiepileptic drug due to its favorable properties and low interactions (no Level I evidence against phenytoin) (7). Initial levetiracetam dosage is 1000-4000 mg/day, up to 5000 mg/day tolerated (8). Phenytoin dosage is 300-500 mg/day, with levels 10-20 mg/dL, taking 7-10 days for steady state (9). Post-surgery seizure prognosis depends on resection extent, pre-op control, and seizure type. Total resection with pre-op control leads to better outcomes (10). Corticosteroids manage tumor symptoms and edema. Starting dose is 16 mg/day, adjusted based on patient (11). Monitoring follows steroid tapering. For surgery without significant edema, steroids control post-op edema but cause side effects. In radiation cases, low-dose steroids (2-8 mg/day) ease radiation-induced edema.

1.3 Diagnostic Neuroimaging for Gliomas

Magnetic resonance imaging (MRI) of LGGs provides distinct visual cues: lesions appearing isointense/hypointense on T1-weighted images, displaying a uniform hyperintensity on T2-weighted images, and notably lacking in contrast enhancement (Fig. 1) (12).

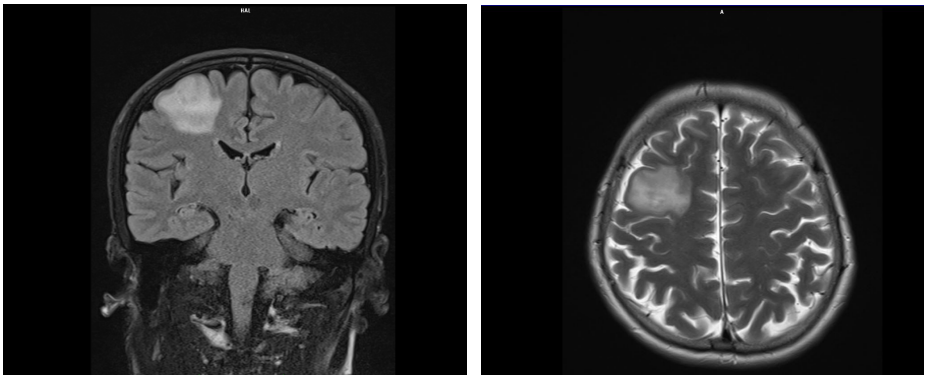

Figure 1

Around 20% of cases exhibit calcifications, manifesting as hyperintense on T1-weighted and hypointense on T2-weighted images (13). Vasogenic edema and necrosis are infrequent due to the indolent growth rate. Employing advanced MRI techniques such as MR spectroscopy contributes to the differentiation of glioma grades (figure 2) and enables the detection of LGG-specific mutations, including IDH1 (14). Both FDG-PET and FLT-PET serve as effective tools to assess LGG metabolism and proliferation, boasting robust positive and negative predictive values (12, 13). Furthermore, perfusion MRI leverages

relative cerebral blood volume (rCBV) to forecast LGG histology with notable sensitivity (80-95%) and specificity (94-96%) (2). The utility of diffusion tensor imaging (DTI) emerges in the differentiation of varying grade histologies, achieving sensitivity of 92-94% and specificity of 53-54% (8, 9).

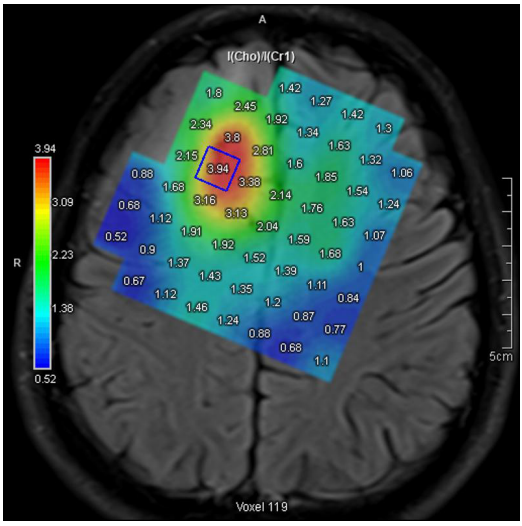

Figure 2: MR spectroscopy Cho/Cre

Functional MRI (fMRI) facilitates the creation of preoperative functional maps, an essential aid in surgical planning. In parallel, magnetoencephalography (MEG) provides heightened temporal resolution for mapping the motor cortex and sensory pathways (15). MEG's advantage is particularly apparent near tumors, as it accurately identifies functional cortices. Additionally, the integration of MEG data with DTI insights augments surgical navigation (15). Another innovative approach, magnetic source imaging (MSI), capitalizes on magnetoencephalographic observations of speech-related neuromagnetic fields, offering a valuable tool for somatosensory cortex mapping and hemispheric dominance determination. This technique has the potential to replace traditional methods like the Wada test (16).

1.4 Prognostic Factors, Patient Outcome, and Survival

In a prospective trial involving WHO grade 2 astrocytomas, oligodendrogliomas, or mixed oligoastrocytomas, certain factors were linked to an elevated risk of tumor recurrence. These factors included preoperative

maximal tumor diameter of 4 cm or larger, astrocytoma/oligoastrocytoma histologic subtype, and postoperative residual tumor diameter of 1 cm or larger (17). Researchers at the University of California, San Francisco (UCSF), conducted a retrospective study of 256 patients and developed a scoring system to predict patient overall survival (OS) and progression-free survival (PFS) (18). This scoring system assigned 1 point each for tumor location within eloquent cortices, Karnofsky Performance Scale score of 80 or lower, age over 50 years, and maximal tumor diameter over 4 cm. Higher scores correlated with worse prognosis. Both Cox proportional hazard modeling and Kaplan-Meier survival curves indicated that a higher score was associated with reduced patient OS and PFS. Patients with a UCSF score of 0 to 1 exhibited a 97% 5-year survival rate, while those with a score of 3 to 4 showed a 5-year survival rate of 56%. An extensive analysis of pooled data from phase 3 clinical trials by the European Organisation for Research and Treatment of Cancer, the Radiation Therapy Oncology Group, and the North Center Cancer Treatment Group (EORTC/RTOG/NCCTG) further delineated prognostic factors for WHO grade 2 gliomas (19). Factors negatively affecting PFS and OS included impaired baseline neurologic status, shorter time since first symptoms (<30 weeks), astrocytic histology, and maximal tumor diameter greater than 5 cm. Early radiation therapy improved PFS but didn't impact OS. This analysis established and validated low, intermediate, and high-risk groups, aiding in accurate prognostication and serving as a tool for stratification in future LGG studies. Another extensive retrospective study encompassing 1097 patients aimed to identify prognostic factors for WHO grade 2 glioma (20). Among 674 patients undergoing initial resection, only 11.9% achieved gross total resection, while 38.9% underwent subtotal resection. The best outcomes were seen in surgical patients with confirmed gross total resection by postoperative imaging, with no signal abnormality recurrence for at least 4 years. Stereotactic biopsy had a 2.8% morbidity rate, and no deaths were recorded. Of surgically treated patients, 58% experienced recurrence within a median timeframe of 35 months. Remarkably, 69% of these recurrent tumors progressed malignantly to higher-grade gliomas. Independent prognostic factors included tumor size, location, neurologic status, and patient age, corroborating previous findings (20).

1.5 Genetic Expression Profile

Unveilin the genetic landscape of LGGs is of paramount importance to unravel the intricate evolution of these tumors (21). TP53 mutations, identified

in nearly two thirds of low-grade astrocytomas, emerge as an early genetic aberration, hinting at the inactivation of this tumor suppressor gene as a pivotal event in glioma genesis(22). Tumors harboring TP53 mutations often progress towards secondary glioblastomas, underscoring the critical role of the p53 protein in cell-cycle arrest, DNA repair, and apoptotic initiation in response to genetic damage. This importance is further highlighted in cases of Li-Fraumeni syndrome, marked by germline TP53 mutations and a heightened cancer incidence, including gliomas (23). Additionally, MGMT gene methylation, linked to resistance against alkylating chemotherapy in high-grade gliomas, aligns more frequently with TP53-mutated tumors, showcasing its interaction with the genetic landscape (24).

As LGGs evolve, gathering additional mutations in genes such as PTEN and PDGFR, they traverse the path towards high-grade malignant gliomas, known for their bleak prognosis. The significance of allelic loss on chromosomes 1p and 19q surfaces, with 50% to 80% of oligodendrogliomas displaying this feature, correlated with heightened chemotherapy responsiveness and improved prognostic outcomes (1, 25). Proposed mechanisms, such as the t(1;19)(q10;p10) translocation, underscore this correlation and its associated benefits. Furthermore, this genetic signature acts as a compass for treatment choices, guiding combined treatment strategies (26).

IDH1 and IDH2 mutations, frequently encountered in LGGs, are another cornerstone of their genetic makeup (27). These mutations often pave the way to secondary glioblastomas, accounting for a notable fraction of all glioblastoma cases. The influence of these mutations is evidenced by their association with younger patient age and better median survival. While IDH1 mutations align with TP53 mutations in astrocytic tumors, they are rarely coupled with chromosome 1p/19q co-deletion, contrasting the scenario observed in oligodendrogliomas. This hint of mutual exclusivity points to IDH mutation's pivotal early role in glioma formation across both astrocytic and oligodendroglial lineage (27). WHO 2016 states that by utilizing the fundamental molecular and clinical distinctions present between IDH-mutant and IDH-wild type diffuse astrocytomas, IDH-wild type astrocytomas exhibit a more aggressive clinical course compared to those with IDH-mutant variants. This fundamental differentiation remains valid in the WHO 2021 classification. In adults, cases of grade 2 and 3 IDH-wild type astrocytomas among diffuse gliomas have been observed to manifest an aggressive clinical trajectory, with patient survival durations almost equivalent to IDH-wild type glioblastomas, which are grade 4 tumors. Hence, within the

cIMPACT studies, it has been collectively agreed that despite histology being grade 2 or 3 according to WHO criteria, IDH-wild type diffuse astrocytic tumors displaying an aggressive clinical course and possessing epidermal growth factor receptor (EGFR) amplification and/or TERT promoter mutation and/or genotype with chromosome 7 gain and chromosome 10 loss should be appropriately termed as WHO grade 4. Consequently, in the WHO 2021 classification, IDH-wild type diffuse gliomas, meeting the histopathological or molecular criteria defined in the classification, are labeled as glioblastoma, IDH-wild type grade 4, and the concept of IDH-wild type grade 2 or 3 astrocytoma is not included in the classification (3).

Additional genetic factors contribute nuanced subtypes to LGGs. ATRX mutations, implicated in maintaining telomere homeostasis, are prevalent in WHO grade 2 gliomas, particularly in oligodendrogliomas. Interestingly, these mutations are absent in grade I pilocytic astrocytomas. CIC and FUBP1 mutations surface mainly in oligodendrogliomas, enriching the spectrum of genetic diversity (28). The presence of ATRX mutations with TP53 and IDH alterations sparks ALT pathway activation, influencing glioma progression and survival (28).

This genetic complexity is not set in stone, as LGGs' genetic profiles shift in response to therapies. Insights from genomic analysis reveal that recurrent LGGs often stem from initial tumors but do not retain the complete set of mutations present in the primary tumor. This phenomenon underscores the influence of treatment strategies, such as temozolomide, on the evolutionary pathway of these tumors. Dynamic genetic alterations, including hypermutation and temozolomide-induced signature mutations, paint a picture of LGGs' adaptation in the face of treatment challenges (29).

1.6 Treatment Options

1.6.1 Observation

It's becoming rarer to simply monitor patients with presumed LGGs based on clinical and imaging characteristics, especially without an initial histologic diagnosis. Some still support this cautious approach for deep-seated or functionally critical lesions where surgery poses higher risks. Although it delays treatment-related risks and costs, it increases the chances of tumor progression, new neurological deficits, or malignant transformation (30).

However, there's a risk of misdiagnosis, and tumor growth can be unpredictable. This approach also brings emotional stress due to uncertainty.

Limited evidence supports observation as a sole strategy for LGGs. Small studies didn't find major differences in outcomes or quality of life between observed and immediately treated patients. Yet, these findings aren't widely applicable due to small sample sizes (31).

Modern studies are lacking, so management decisions depend on overall clinical assessment and surgeon's experience. If observed, disease progression could manifest as new neurological deficits, changing seizure patterns, increased lesion size, or new contrast enhancement on MRI.

1.6.2 Stereotactic Biopsy

Surgical options for LGG patients encompass open resection and stereotactic biopsy, contingent on clinical status, tumor location, and surgeon preference. Surgical goals include diagnosis, symptom relief, mass effect reduction, and tumor cytoreduction (32). For suspected or known non-optic pathway supratentorial LGGs in adults, the standard is to obtain a tissue diagnosis before active treatment begins. Stereotactic biopsy is now less common but still useful for uncertain cases, although tumor heterogeneity can lead to diagnostic inaccuracies (33). Biopsy planning could benefit from targeting enhancing regions seen on imaging, especially for lesions with focal enhancement. Surgical risks with frameless stereotactic biopsy are generally low, with less than 1% morbidity and mortality rates, mainly associated with high-grade lesions. Choosing surgery or observation depends on clinical symptoms. A Norwegian study compared biopsy-focused centers to early resection-focused centers for diffuse LGG patients. After follow-up, 52% under biopsy and monitoring had died compared to 32% under early resection (34). However, randomized controlled trials are lacking to favor one approach over the other (35).

1.6.3 Microsurgical Resection

In cases of accessible LGGs with symptoms like local mass effect, increased intracranial pressure, and intractable seizures, microsurgical resection plays a pivotal role. This procedure serves various purposes, including relieving mass effect, performing cytoreduction, and aiding in diagnosis. Cytoreduction can also have positive effects on cerebral edema and potentially enhance the tumor's responsiveness to radiotherapy and chemotherapy. The extent of tumor removal achieved through open surgical resection offers the added advantage of providing more tissue for histologic analysis, thereby improving the accuracy of the pathological diagnosis (18).

The rationale behind cytoreduction lies in its potential to reduce the number of tumor cells that are susceptible to accumulating additional genetic abnormalities, consequently lowering the risk of tumor progression and malignant transformation. The application of open surgical interventions in treating LGGs adheres to general principles of neurosurgical tumor procedures. Modern neurosurgical techniques such as ultrasonography, functional mapping, frameless navigational resection devices, and intraoperative imaging modalities empower neurosurgeons to achieve more comprehensive resections while minimizing associated morbidity (36).

Intraoperative ultrasonography offers real-time insights during surgery, aiding in tumor detection, margin delineation, and distinguishing tumor tissue from surrounding peritumoral edema, cysts, necrosis, and normal brain tissue. While its effectiveness is limited by artifacts from blood and surgical trauma at the resection margin, post-resection tumor volume based on intraoperative ultrasonography correlates significantly with tumor volume assessed through postoperative MRI. Intraoperative MRI also plays a potential role, particularly when distinguishing infiltrated tumor tissue from normal tissue is challenging (37).

Stimulation mapping techniques are vital for minimizing postoperative morbidity and achieving radical resections, especially when dealing with tumors located around functionally significant cortical and subcortical areas. These mapping techniques help identify functional regions within these eloquent territories, reducing the likelihood of postoperative deficits. Awake language mapping becomes crucial due to variations in the localization of language pathways. In cases where tumors are situated in the dominant hemisphere near critical areas like the frontal operculum, temporal lobe, or angular gyrus, language mapping can guide the surgical approach (38).

During the resection process, caution is warranted even when tumor margins are clear, as functional brain tissue may exist within the tumor itself. Achieving a balance between the extent of resection and functional preservation is imperative. Numerous retrospective and prospective studies have established a positive correlation between the extent of resection and patient outcomes, including overall survival. These findings underscore the importance of maximal resection with minimal morbidity.

In summary, microsurgical resection plays a crucial role in treating accessible LGGs with symptomatic presentations. The procedure helps alleviate mass effect, perform cytoreduction, and aid in diagnosis. Contemporary

neurosurgical techniques enable extensive resections with reduced morbidity. The extent of resection has been consistently linked to improved patient outcomes and prolonged time to malignant transformation. While techniques like intraoperative MRI and fluorescence-guided surgery hold promise, they are still in the investigational phase.

1.7 Radiotherapy

Postoperative radiation treatment has shown benefits in patients with LGGs. While it doesn't significantly increase overall survival (OS) compared to observation alone, it does offer improved progression-free survival (PFS), as demonstrated by the European Organisation for Research and Treatment of Cancer (EORTC) 22845 trial. This trial utilized a lower radiation dose of 54 Gy, which proved more favorable than higher doses in terms of side effects and survival rates (39).

Common side effects of radiation treatment included dermatitis, alopecia, and lethargy. The EORTC 22845 trial also revealed that patients initially observed and later given salvage radiation had comparable OS to those initially treated with radiation. In an international trial (EORTC 22033-26033), patients with high-risk or progressive LGGs were randomly assigned to radiation or chemotherapy with temozolomide (TMZ). Results showed no PFS difference between the arms, but immediate TMZ treatment improved OS in patients with 1p-deleted tumors. Low-dose radiation at 50.4 Gy maintained neurocognitive outcomes for years post-treatment (40-42).

1.8 Chemotherapy

Chemotherapy options for treating LGGs include TMZ and PCV. TMZ is an oral agent that disrupts DNA replication and cell division, primarily affecting rapidly dividing cells. PCV, comprising procarbazine, CCNU/lomustine, and vincristine injections, is another chemotherapy regimen. Chemotherapy is sometimes used for recurrent cancer and may be combined with radiation (43).

A randomized phase 3 study by the Radiation Therapy Oncology Group (RTOG) explored postoperative radiotherapy (RT) with or without PCV in high-risk LGG patients. The RT plus PCV arm showed significantly longer median survival and PFS compared to RT alone. Survival rates at 5 and 10 years were higher with RT + PCV. For grade 2 gliomas with limited resection or age over 40, PCV + RT extends OS and PFS (43).

A phase 2 trial investigating TMZ response in LGGs revealed a 10% partial response rate. Response was better in LGGs with 1p/19q deletions. The EORTC 26971 trial focused on first-line TMZ treatment for recurrent oligodendrogliomas, showing over 50% response rate (44).

MGMT promoter methylation also impacts chemotherapy response. A study with 1p/19q deletions found that MGMT methylation improved survival outcomes with prolonged TMZ dosing. Neoadjuvant TMZ treatment before surgery in eloquent brain areas reduced tumor growth and improved surgical outcomes. (45) In conclusion, chemotherapy, particularly TMZ and PCV, plays a significant role in treating LGGs, especially in cases of recurrence or specific genetic markers (46).

1.9 Conclusion

Advancements in diagnosis, treatment, and genetics are reshaping LGG management. Genetic and clinical data help tailor treatments for better outcomes. Biopsies offer grade info, guiding decisions. Maximized tumor removal delays recurrence, aided by intraoperative mapping. Chemo and radiation combo extends survival. Challenges remain due to LGG diversity and genetics. Future trials may lead to personalized treatments for improved results.

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CHAPTER V

ADULT TYPE HIGH GRADE DIFFUSE GLIOMAS

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1. Adult Type High Grade Diffuse Gliomas

1.1 Classification and Epidemiology

Gliomas are prominent as the most common primary brain tumors. In the United States, they constitute 80% of all malignant primary brain and central nervous system tumors, with an annual age-adjusted incidence rate of 5.55 per 100,000 individuals (1).

Prior to the incorporation of molecular markers into the World Health Organization (WHO) classification, gliomas were classified based on their morphological and histopathological characteristics. However, since the identification and further elucidation of molecular features in the WHO 2016 classification, a layered and comprehensive diagnostic approach has been adopted for diffuse gliomas and several other cerebral tumors. This fundamental alteration in strategy indirectly highlights that tumors with similar or even indistinguishable histopathological appearances may exhibit distinct molecular mutation patterns and, most crucially, result in different clinical outcomes.

Towards the end of 2016, ahead of the introduction of a fresh classification system for central nervous system (CNS) tumors by the WHO, cIMPACT-NOW (the Consortium to Inform Molecular and Practical Approaches to SSS Tumor Taxonomy-Not Officially WHO) was established by a consortium of experts in neuropathology and neurooncology. The intention was to evaluate the recommended alterations in future classifications of CNS tumors and

provide pragmatic recommendations. These updates, which included well-established molecular parameters in the classification of diverse gliomas, aimed to guide experts and potentially establish a cornerstone for forthcoming WHO classifications. The subsequent update spotlighted H3K27M mutant tumors and IDH mutant diffuse glial tumors, while the subsequent update centered around the molecular attributes of IDH-wild type glioblastoma (2, 3). The final three updates, conducted in 2020, encompassed the grading criteria and terminology for IDH-mutant astrocytomas, along with novel principles for the future classification and grading of CNS tumors grounded on the cIMPACT-Utrecht conference (4). Subsequently, the 2021 WHO classification was unveiled. According to this classification, high-grade diffuse gliomas in adults can be distinguished as IDH-mutant grade 3 and 4, oligodendroglioma grade 3, and glioblastoma, IDH wild type, grade 4. Remarkably, IDH-wild type astrocytomas are categorized within the grade 4 group, whereas IDH-mutant astrocytomas are assigned to grades 3 and 4.

In 2016, the WHO, leveraging fundamental molecular and clinical distinctions between IDH-mutant and IDH-wild type diffuse astrocytomas, asserted that IDH-wild type astrocytomas manifest a more aggressive clinical trajectory in comparison to their IDH-mutant counterparts (3). For adults affected by diffuse gliomas, it has been observed that IDH-wild type astrocytoma grade 2 and 3 cases mirror an aggressive clinical course and almost identical survival durations as those with IDH-wild type glioblastoma grade 4 (5). Consequently, through cIMPACT studies, consensus has been achieved that IDH-wild type diffuse astrocytic tumors should be ascribed the WHO grade 4 label if they demonstrate histological features of WHO grade 2 or 3, and exhibit TERT promoter mutation and/or epidermal growth factor receptor (EGFR) amplification and/or chromosome 7 gain-chromosome 10 loss genotypes. Thus, in the WHO 2021 classification, IDH-wild type diffuse gliomas are designated as glioblastoma, IDH-wild type grade 4 when specific histopathological or molecular criteria are met, while the concept of IDH-wild type grade 2 or 3 astrocytoma is omitted from the classification (6).

High-grade gliomas are present in people across all age brackets, but their prevalence tends to increase with advancing age. Genetic conditions such as the Li-Fraumeni cancer syndrome linked to germ line mutations in the TP53 gene, alongside syndromes like neurofibromatosis and Turcot syndrome, have been implicated in the genesis of high-grade gliomas. However, these conditions represent less than 5% of all high-grade gliomas. Factors like age and an

individual's performance status stand as crucial determinants for prognosis in these gliomas. For glioblastoma patients, the average survival spans roughly 16 to 18 months, while it extends to 2 to 5 years for those with grade 3 astrocytoma possessing IDH mutations, and about 3.5 years for patients with grade 3 oligodendroglioma. Common treatment modalities consist of surgical excision followed by both radiation therapy and chemotherapy. Despite the enhanced understanding of gliomas' molecular characteristics in recent times not leading to marked breakthroughs in clinical trial outcomes and the efficacy of newer therapeutic agents remaining limited, such knowledge has paved the way for more accurate patient classification via genomic analysis.(7)

1.2 Pathogenesis

The pathogenesis of gliomas still largely remains an enigma. It is probable that the originating cell is a neuroglial precursor cell. It has been understood that IDH gene mutations emerge early in glioma formation. Mutant IDH proteins trigger genome-wide methylation, thus expediting tumor formation. Additionally, mutations in the p53 (TP53) gene are observed early in malignant astrocytic tumors (8). Due to the difficulty in diagnosing tumors such as glioblastomas, which are IDH wild type and therefore challenging to diagnose early, the identification of molecular and genetic differences is complex.

In IDH mutant grade 3 astrocytomas, among the molecular abnormalities, there is a presence of 17p heterozygous loss (50-60%), 10q loss (35-60%), and 19q loss (40-50%). Glioblastomas, on the other hand, are characterized by EGFR amplification (40-50%) associated with EGFRvIII mutation in approximately half of these patients. Furthermore, cell cycle control is disrupted in most glioblastomas, either at the receptor tyrosine kinase signaling pathway level (88%), the p53 signaling pathway level (87%), or the retinoblastoma signaling pathway level (78%).

IDH mutations associated with gliomas are gain-of-function mutations in the metabolic enzymes IDH1 and IDH2, resulting in the excessive production of the oncometabolite 2-hydroxyglutarate. The majority of IDH-mutant diffuse astrocytomas also harbor loss-of-function mutations in TP53 and ATRX (9). ATRX encodes a significant chromatin-binding protein, and its deficiency is linked to epigenomic alterations and telomere dysfunction. ATRX mutations and alternative lengthening of telomeres mutually interact with activating mutations in the TERT gene, which encodes the catalytic component of telomerase. TERT

mutations are prevalent in the majority of oligodendrogliomas and IDH-wild type glioblastomas.

The homozygous deletion of CDKN2A/B genes has been identified as a poor prognosis marker in IDH-mutant diffuse astrocytic glioma cases (3). An IDH-mutant astrocytoma with high mitotic activity and histological anaplasia but lacking microvascular proliferation, necrosis, or CDKN2A/B homozygous deletion corresponds to the definition of 'Astrocytoma, IDH-mutant, grade 3.' IDH mutant astrocytomas with microvascular proliferation, necrosis, or CDKN2A/B homozygous deletion or any combination of these features are classified as WHO grade 4.

1.3 Clinical Features and Diagnosis

High-grade gliomas present symptoms according to their brain location. Specifically, glioblastomas grow rapidly, causing patients to display certain neurological symptoms like aphasia, hemiparesis, and visual field disturbances. Seizures are common in oligodendroglioma patients. There might also be observable changes in behavior and cognitive functions. Headaches can arise from intratumoral bleeding. When these gliomas have a significant mass effect, it can increase intracranial pressure, causing nausea, vision irregularities, vomiting, and more headaches. To diagnose these gliomas, MRI is preferred over CT scans. Usually, MRI images of these gliomas reveal areas with different gadolinium enhancements, surrounded by T2 signal alterations due to swelling and infiltration. Sometimes, there can be signs of bleeding or zones with limited diffusion. There are instances where tumors have several centers and may even cross the midline. Importantly, grade 3 gliomas can sometimes look like grade 2 gliomas on radiographic studies, showing little or no gadolinium contrast enhancement on MRI. Leptomeningeal spread or drop metastases are rare at diagnosis, so spinal MRI scans are not frequently done unless driven by particular clinical concerns. While MRI is crucial for diagnosing high-grade glioma, the final verification comes from a pathological review after surgery or a biopsy.

2.1 IDH-Mutant Astrocytoma of Grade 3 and 4

Typified by mutations either in IDH1 (R132H, situated on chromosome 2) or in IDH2 (R172K, situated on chromosome 15), are essentially astrocytomas with a diffused infiltration pattern. Predominantly affecting younger adults, these tumors are present across the central nervous system but predominantly

surface in the frontal lobes. The incidence skews higher in males, with a ratio of 1.5:1 compared to females. This mirrors the tendencies seen in IDH mutated oligodendrogliomas with 1p/19q co-deletion, bolstering theories about their origins from precursor cell groupings (6). Seizures emerge as the principal symptom. MRI scans frequently depict T1-hypointensity combined with T2-hyperintensity, indicative of expanding tumor regions during its nascent stages. As these diffuse astrocytomas evolve, they might display characteristics of contrast uptake and even develop into grade 3 IDH mutated astrocytomas, further progressing to grade 4 malignancies. A distinguishing feature of infratentorial IDH-mutant gliomas is their molecular and clinical differentiation from other similar gliomas. They possess mutations beyond the typical IDH1 R132H, and though ATRX mutation rates are on the lower side, they may carry the H3K27M mutation. Relative to their supratentorial counterparts, infratentorial tumors associated with IDH mutations exhibit a less favorable prognosis (10).

2.2 Oligodendroglioma Grade 3

Astrocytomas make up between 80-90% of all gliomas, with oligodendroglioma ranking as the second major CNS cancer, covering just 5-6% of the total gliomas (11). They are most commonly observed in individuals aged 35-44. Roughly two-thirds of these patients report seizures as their first symptom. The frontal lobe is the usual location of these tumors. Key characteristics of oligodendrogliomas are their unique “fried egg” appearance, proliferation of neoplastic cells resembling oligodendrocytes in both the cortex and white matter, paired with mucoid or cystic changes and microcalcifications (12).

For diagnosis, the current WHO guidelines mandate the detection of IDH1 or IDH2 mutations. This often involves using the R132H-mutant IDH1-specific antibody in immunohistochemistry or DNA genotyping, especially when the immuno-test fails to recognize the R132H-mutant IDH1. Additionally, the 1p/19q codeletion must be confirmed using techniques like FISH or other molecular genetic tests. Notably, mutations in the CIC gene (located on 19q13.2) and FUBP1 (on 1p31.1) can be defining elements. While oligodendrogliomas typically don’t have ATRX mutations, they regularly showcase activating mutations in the TERT promoter, which boosts TERT expression. Thus, if an IDH-mutated tumor has an astrocytic appearance and its ATRX/p53 immunohistochemistry matches with astrocytic mutations (such as in ATRX or TP53), the 1p/19q assessment isn’t required (13).

For WHO grade 3 anaplastic oligodendroglioma, defining features include anaplastic histological attributes. Special attention has been given to the prominence of microvascular proliferation and an increase in mitotic activity as signs of oligodendroglioma anaplasia. Over 70% of tumors at this grade exhibit contrast enhancement. Studies have shown that a 1p/19q codeletion in patients treated with supplemental radiation and chemotherapy often aligns with a better outcome and extended life expectancy. Further research points towards a prolonged median survival rate for anaplastic oligodendroglioma patients undergoing both treatments (14).

2.3 Glioblastoma, IDH-wild type, Grade 4 Astrocytoma

In adults, it is most commonly seen, being 1.6 times more prevalent in men. A myriad of environmental and genetic elements has been studied as potential causes for glioblastoma. Up to this point, the only confirmed risk factor is ionizing radiation to the head and neck. There's no definitive evidence supporting the role of environmental factors, toxins, infections, mobile phone usage, or head trauma (15). The frequency of occurrence decreases in individuals with a history of allergies or atopy. Glioblastoma is most commonly observed in the subcortical white matter of the cerebral hemispheres. It's characteristic for glioblastoma to show rapid invasion into neighboring brain structures. The infiltration predominantly occurs along the white matter pathways but can also encompass cortical and deep gray structures. When the infiltration grows across the corpus callosum into the opposite hemisphere, the result can be a bilateral, symmetrical lesion often referred to as "butterfly glioma". Symptoms largely depend on the tumor's location, primarily manifesting as focal neurological deficits and edema alongside increased intracranial pressure. Half of all patients initially present with a seizure. On MRI imaging, glioblastomas appear irregularly shaped with a ring-like contrast uptake surrounding a central necrotic area. In 2021, the WHO updated the term "glioblastoma" to "IDH-wild type grade 4 astrocytoma". Typically, glioblastoma consists of highly cellular glioma, often showing poor differentiation and sometimes made up of pleomorphic tumor cells with nuclear atypia and significant mitotic activity. Tumor necrosis is a fundamental characteristic of glioblastoma. In recent studies, findings such as EGFR amplification, TERT promoter mutations, and either whole chromosome 7 gain or whole chromosome 10 loss are diagnostic for glioblastoma even in the absence of histopathologic features. CDK4 amplification, MDM2 amplification, MET amplification, PDGFRA amplification or mutation, and FHFR3 fusion are

molecular features that support a glioblastoma diagnosis. (10) Microvascular proliferation is also observed in glioblastomas, ranking them among the most vascularized of all tumors. Under light microscopy, this proliferation is typically evident in multilayered mitotically active endothelial cells with smooth muscle cells/pericytes.

3. Prognostic Markers

Recent genomic analyses have identified several molecular markers associated with prognosis, aiding in predicting clinical outcomes for cases with glioma. Some of these markers assist in distinguishing gliomas that are challenging to differentiate based solely on histology, and they aid in anticipating both outcomes and responsiveness to specific treatments. Notable molecular markers of prognostic significance for high-grade gliomas include: 1p/19q co-deletion, IDH1/IDH2 mutations, MGMT (O-6-methylguanine-DNA methyltransferase) promoter methylation, EGFR amplification, TERT mutation, and alterations in chromosomes 7 and 10, as well as CDKN2 A-B (16).

Despite aggressive surgical resection, radiation therapy, and chemotherapy, glioblastoma remains notoriously resistant to treatment due to minimal improvements in survival rates. The MGMT promoter methylation stands as the sole predictive biomarker for the efficacy and response to alkylating and methylating chemotherapy agents in glioblastoma.(17) The MGMT gene codes for a DNA repair protein that negates the alkylation at the O-6 position of guanine, thus reversing the damage caused by alkylating chemotherapeutic agents like temozolomide. Abnormal methylation of the MGMT gene promoter leads to gene silencing, reducing the tumor cells' ability to repair DNA damage induced by alkylating agents (17, 18). A pivotal study that set radiation in combination with temozolomide as the standard treatment for patients with glioblastoma showed a significant survival increase in patients treated with temozolomide, demonstrating both its prognostic and predictive value. This significance has been confirmed in various other studies for both glioblastoma and anaplastic gliomas. Notably, findings from the European Organization for Research and Treatment of Cancer (EORTC) suggest the predictive biomarker role of MGMT promoter methylation specifically in anaplastic oligodendrogliomas and oligoastrocytomas (19, 20). However, another study suggests its predictive significance is limited only to tumors with IDH1-wild type. IDH mutations are linked with favorable prognosis in high-grade gliomas (21). Glioblastomas with IDH1 mutations are now recognized as representing a distinct tumor in terms of

phenotypic, epigenetic, and genomic presentations when compared to IDH-wild type glioblastomas. IDH2 mutations are less frequent in gliomas (22). TERT mutations are found in 70% of glioblastoma, IDH wild type cases, and in 95% of oligodendroglioma, IDH mutant with 1p/19q co-deletion cases, playing a role in tumor pathogenesis.

Homozygous deletion of CDKN2A/CDKN2B indicates poor prognosis for grade 4 IDH mutant astrocytomas. These genes encode cyclin-dependent kinase inhibitor proteins and play roles in Rb1 and p53 related signaling pathways. Gains in chromosome 7 lead to overexpression of genes like PDGFA and EGFR, influencing tumor development (3). Losses in chromosome 10 affect tumor suppressor genes like PTEN and MGMT. Both the gain in chromosome 7 and loss in chromosome 10 serve as molecular markers for glioblastoma, IDH wild type, WHO grade 4 cases. Heterozygous loss in chromosomes 1p and 19q in anaplastic oligodendrogliomas correlates with treatment response and survival. Two large studies have highlighted the predictive and prognostic value of 1p/19q co-deletion (23). Importantly, according to the 2016 WHO classification, the diagnosis of oligodendroglioma requires the demonstration of both the 1p/19q co-deletion and IDH mutation.

4. Treatment

In recent times, therapeutic approaches to high-grade gliomas have witnessed advancements, but pivotal treatment remains anchored in extensive surgical resection complemented by radiation and chemotherapy. For glioblastoma, a combination of temozolomide with external radiation emerges as a standard regimen, underpinned by Level I evidence from a phase 3 randomized clinical study (18). However, the best therapeutic strategy for grade 3 gliomas is still a topic of discussion.

4.1 Surgical Intervention

The primary intent of surgical intervention is the maximal and safe removal of tumor tissue utilizing microsurgical modalities without jeopardizing neurological outcomes. In high-grade glioma management, complete surgical resection stands as the best practice. Such a resection offers not only a pathological validation of the diagnosis but also enables detailed genomic and molecular assessments of the tumor tissue. Moreover, excising the tumor alleviates mass effects and can enhance neurological conditions. Complete resection of contrast-absorbing tumor regions is advised in cases of high-grade

gliomas. Historical data suggests a correlation between the thoroughness of resection and patient prognosis, showcasing significant survival benefits with more comprehensive resections (24, 25). Employing techniques like functional MRI, diffusion tensor imaging, and surgical navigation systems, complemented by tools such as intraoperative MRI, ultrasonography, functional monitoring, and 5-aminolevulinic acid (5-ALA) for fluorescent tumor marking, surgeons can optimize resection outcomes while minimizing potential neurological impairments (26). Tools like intraoperative MRI-aided neuronavigation are invaluable, offering insights like shifts in midline structures and providing a real-time view of the tumor being excised. Intraoperative ultrasonography furnishes real-time visuals of the tumor and surrounding surgical areas, aiding the surgeon in the process (27). Employing awake surgeries, with the patient under local anesthesia, allows for real-time linguistic and cognitive feedback, and leveraging tools like evoked potentials, electromyography, or brain mapping can be pivotal in surgeries involving critical brain regions (28). The merits of resecting recurrent tumors in relation to survival outcomes remain debatable. However, it can offer diagnostic clarity between genuine disease progression and pseudoprogression, while also diminishing mass effects. Pseudoprogression, characterized by enhanced tumor contrast following therapy, typically regresses over time without therapeutic intervention. Historical data underscores the survival benefits associated with comprehensive resections in subsequent surgeries (29). Notably, in recurrent glioblastoma scenarios, cases involving critical brain regions or with lower Karnofsky performance scores, or those with a tumor volume exceeding 50 cm^3, were associated with reduced post-surgery survival. Yet, another study highlighted better outcomes in patients with a Karnofsky score exceeding 70 and devoid of ependymal contrast (30). The FDA, in 2017, approved 5-aminolevulinic acid (5-ALA) as an intraoperative imaging agent, enabling real-time tumor visualization through fluorescence-guided surgery (31). Upon metabolism, 5-ALA transforms into protoporphyrin IX, radiating light within the tumor cells at a fluorescent wavelength (32). Data from studies on high-grade glioma patients have emphasized the merits of using 5-ALA, pointing to enhanced tumor resection rates and better progression-free survival outcomes in comparison to traditional methodologies. Follow-up research has suggested that surgeries utilizing 5-ALA fluorescence result in reduced residuals compared to conventional techniques, indicating a favorable prognosis . Notwithstanding its benefits, the short half-life (approximately 3 hours) and an increased rate of resection pose challenges with 5-ALA

fluorescence-guided surgeries. While it's paramount to ensure resections don't trigger new neurological deficits, there's a growing sentiment suggesting benefits with supramarginal resections in certain cases. The fluorescence-guided microsurgery leveraging 5-ALA has gained traction, contributing significantly to enhanced resection rates and consequently better survival outcomes. Surgical interventions can also serve as a medium for therapeutic molecule delivery. BCNU-infused biodegradable agents have shown promise in reducing contrast-enhancing volumes in both recurring and newly diagnosed high-grade gliomas (33, 34). Several cutting-edge therapeutic techniques, such as viral gene therapy, oncolytic viruses, and radio-labeled antibodies, can be seamlessly integrated with surgical interventions.

4.2 Radiotherapy

Radiotherapy aims to achieve local tumor management without triggering neurotoxic effects. Prognostic indicators like the type of disease, patient age, and existing tumor size guide the decision on the radiotherapy's initiation, dose, and design. It's usually initiated 3-5 weeks post-surgery. Delivering a cumulative dose of 55-60 Gy in daily increments of 1.8-2 Gy (35). Older individuals (>65-70 years) or those with a worse prognosis, typically indicated by KPS less than 70, might benefit from hypofractionated radiotherapy, for example, 15 sessions at 2.67 Gy each.

4.3 Chemotherapy

Starting drug therapy for gliomas or any other condition demands a comprehensive pre-assessment to ensure the patient's overall health is suitable for the intended medication, minimizing potential risks. As described:

4.3.1 Preliminary Assessment:

Blood Values: Monitoring complete blood counts can predict a patient's susceptibility to drug-induced bone marrow suppression.

Liver and Kidney Functions: Essential for drug metabolism and excretion, respectively. Abnormal values might necessitate dose adjustments or alternative therapies.

Cardiopulmonary Health: Some drugs can exacerbate or be contraindicated in heart and lung diseases.

Infections: Patients with active infections might be at a higher risk of complications if a drug has immunosuppressive side effects.

4.3.2 Choice of Drugs for Gliomas:

Temozolomide: Preferred for its ability to penetrate the blood-brain barrier. Myelosuppression, especially thrombocytopenia, is a notable side effect, emphasizing the importance of monitoring liver health and complete blood counts (36).

Nitrosourea-Based Alkylating Drugs: Include lomustine, carmustine, nimustine, and fotemustine. They differ from temozolomide in that their hematologic toxicities are often cumulative and manifest later.

Fotemustine: Can require dose adjustments, treatment breaks, or discontinuation due to its side effects.

Carmustine: Apart from hematologic toxicities, it has a potential side effect of lung scarring.

Lomustine: Rarely, it can also lead to lung scarring but is known for being combined with procarbazine and vincristine to make the PCV regimen.

Wafers: Carmustine has been incorporated into biodegradable wafers that can be placed in the surgical cavity post-tumor resection to deliver the drug locally, which has shown promise in some patients with gliomas.

4.3.3 Treatment Efficacy:

Grade 3 Gliomas: The role of chemotherapy, especially temozolomide, in treating grade 3 gliomas is an evolving field. Some research indicates a survival advantage when chemotherapy is added to radiation for specific subtypes of grade 3 gliomas, particularly oligodendrogliomas. However, this combination isn't universally beneficial for all grade 3 gliomas (23, 37).

In summary, the choice of chemotherapy for gliomas is multifaceted, requiring an individualized approach based on tumor type, patient health, and the latest clinical evidence. Regular monitoring during treatment is crucial to promptly detect and manage side effects, ensuring the best possible outcomes for patients.

5. Importance of Targeting Angiogenesis:

Glioblastomas, notably associated with elevated levels of proangiogenic agents such as vascular endothelial growth factor (VEGF), have a pronounced angiogenic nature. Various clinical endeavors have focused on strategies to counteract VEGF, predominantly using monoclonal antibodies and tyrosine kinase inhibitors. In this context, bevacizumab has emerged as a key player. This

drug, dispensed intravenously, follows a dosing regimen of 10 mg/kg every two weeks (38). The FDA has approved bevacizumab both as a monotherapy and in combination with irinotecan (39).

6. Summary

In 2021, the WHO's classification of CNS tumors highlighted several adult-type diffuse gliomas: IDH-mutated grade 3 and 4 astrocytomas lacking the 1p/19q co-deletion, grade 3 IDH-mutant oligoastrocytomas with the 1p/19q co-deletion, and IDH-wild type grade 4 astrocytomas, commonly referred to as glioblastomas, which are grouped in the high-grade glioma classification. The primary therapeutic approach revolves around comprehensive surgical removal, followed by sessions of radiation and chemotherapy. There's a spectrum of views about the best adjunctive therapy specific to tumor variations, with ongoing investigations in this domain. A deeper understanding of their molecular and genetic characteristics aids in refining prognosis and propelling advancements in targeted therapeutic strategies.

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CHAPTER VI

EWING SARCOMA

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1. Introduction

Ewing Sarcoma is the most common primary malignant bone tumor of the pediatric period and is usually seen between the ages of 5-25 (1).

It was first described in 1921 and constitutes 15% of bone sarcomas (2). Like all sarcomas, it originates from mesenchymal cells, mainly from the mesenchymal cells of the bone marrow.

The most common area of origin is the diaphysis of long bones. It belongs to the family of primitive neuroendocrine tumors, also known as small blue round cell tumours (3).

2. Etiology

No environmental factors, radiation exposure, or family history of a similar malignancy have been found to be associated with Ewing Sarcoma. Although it is thought to be due to a gene mutation, this theory has not been proven yet (4).

3. Anamnesis

Patients usually apply to the clinic with complaints of fever and swelling. Therefore, in the first stage, it is confused with osteomyelitis or septic arthritis. When biochemical tests are examined, an increase is seen in ALP, LDH, sedimentation and CRP values (5).

Patients may sometimes present to the emergency room with pathological fractures. There are studies reporting that pathological fracture of the primary bone tumor is considered a poor prognostic factor and even causes amputation to

be preferred as a surgical method. However, there is still no definitive consensus on this factor. However, it should be noted that such fractures should not be treated like a standard fracture (6).

4. Imaging

The first examination requested for imaging purposes must be X-ray radiography. The location, pattern and size of the lesion can be determined on the radiograph. Although the lamellar (onion skin) finding is pathognomonic in Ewing sarcoma, a similar finding is also seen in osteomyelitis **(Figure 1)**. Apart from this, Codman's triangle and hairy periosteal reaction can be seen (7).

Computed tomography (CT) is of critical importance in evaluating the presence of metastases in the lung, as well as better evaluating the bone structure (8).

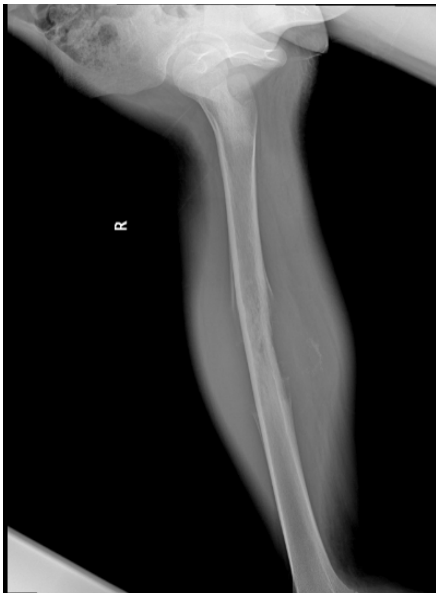

Figure 1: *X-ray Imaging of a Ewing Sarcoma Case at, Diapyseal Region of Femur, Resembling the Onion Skin Sign*

Magnetic resonance imaging (MRI) is the gold standard in the evaluation of tumor lesions **(Figure 2)**. MRI allows evaluation of the bone and soft tissue component of the tumor, its size and relationship with adjacent neurovascular structures, the presence of necrosis and its proximity to the epiphyses (9).

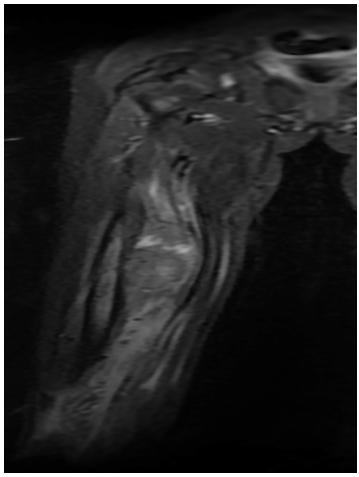

Figure 2: *MRI Imaging of Sağ Femur Typically Showing a Mass Originated From Bone Marrow*

Bone scintigraphy shows the activity in the bone and the presence of involvement in other bones (10).

FDG-PET scanning is very useful in determining the metabolic activity of the tumor and in screening during treatment response and treatment follow-up **(Figure 3)**. While a decrease in SUVmax value is observed in patients who respond well to treatment, MRI helps distinguish lesions with mass appearance from necrotic tissue (11).

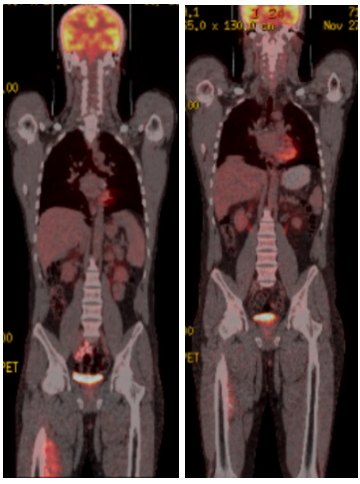

Figure 3: *FDG/PET Body Scan Before and After Neoadjuvant Chemo+Radiation Therapy*

5. Histopathology

Unlike osteosarcoma, osteoid formation is not expected in macroscopic appearance in Ewing sarcoma. Therefore, the tumoral tissue is not as hard as osteosarcoma and chondrosarcoma. Although it originates in the bone marrow, areas where it penetrates the bone cortex can be observed.

Microscopically, small blue round cells are observed, as they are typically from the PNET group. These cells are also seen in retinoblastoma, medulloblastoma, and neuroblastoma. CD99 is stained positively in 90% of cases. However, CD99 can also be stained positively in malignancy types other than Ewing sarcoma (12).

Apart from CD99, positivity may also be observed in CD45 staining. Apart from this, positivity can also be seen with vimentin, S-100, desmin and NSE labeling. However, PCR and FISH tests are often required for definitive diagnosis.

6. Staging

AJCC staging, which is used in all types of malignancy, is also used for Ewing sarcoma. However, Ewing sarcoma also has its own classification. This classification is divided into three as EW-1 intraosseous solitary, EW-2 extraosseous solitary and EW-3 distant metastasis (13).

7. Treatment

In the treatment of Ewing sarcoma, neoadjuvant treatments are primarily applied. Ewing sarcoma is sensitive to neoadjuvant chemotherapy and radiotherapy and they play an important role in reducing tumor size.

Ewing sarcoma often responds well to chemotherapy and the condition manifests itself as reduction in size, regression outside the bone into the bone, and extensive tumor necrosis. Sensitivity to chemotherapy is manifested pathologically by the Huvos classification(14). Necrosis over 90% after neoadjuvant treatment is an indicator of good prognosis. The main agents used in chemotherapy are vincristine, adriamycin, cyclophosphamide, ifosfamide, etoposide and adriamycin(15). Which of these agents will be used may vary depending on the presence of metastasis and response to chemotherapy. Neoadjuvant chemotherapy usually lasts 6 cycles. Early conversion to surgery is due to progression under chemoradiotherapy and negatively affects prognosis and survival(16).

If the tumor is localized in a single area, radiotherapy and chemotherapy are given together. In this way, the tumor burden is reduced and the tumor size decreases, making surgery easier and contributing to the reduction of complications(17).

The decision for surgery depends on the size of the tumor, its relationship with neurovascular structures, and its proximity to the epiphysis or joint line. Since it is generally of diaphyseal origin, reconstruction with bone cryoprezervation and vascularized or nonvascularized fibula graft is preferred(18). Recovered bone is the excision of tumoral bone tissue within wide surgical margins, keeping it in -200 °C liquid nitrogen for 15 minutes and acellularizing it, then passing a fibular graft through the medullary cavity and then fixing it back to the excised space **(Figure 4)**.

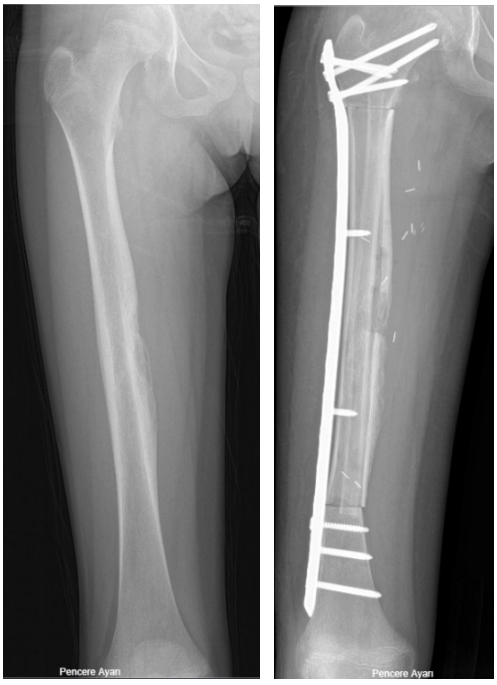

Figure 4: *An Example of Bone Recycling With Vascularized Fibular Graft*

Another option used in tumors originating from the diaphysis is the intercalar prosthesis. This is based on direct placement of a prosthetic material rather than restoring bone(19).

In case of invasion in the joint line, tumor resection arthroplasty is performed because the cartilage will have to be sacrificed. Although the advantage of both

mechanical management methods over the biological method is to provide early weight bearing, this advantage disappears in the long term and complications such as implant-related infection and failure cause its use to be limited to cases where long survival is not expected **(Figure 5)** (20).

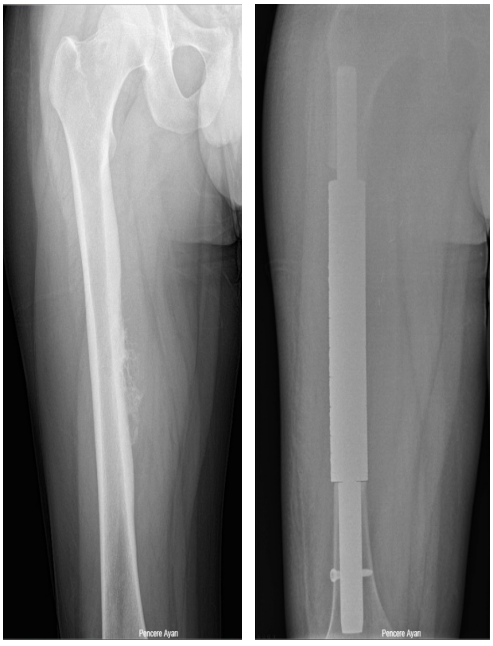

Figure 5: *An Example of Intercalary Prosthesis*

If all compartments are invaded and neurovascular structures cannot be saved, amputation must be used. Although this can also be used as a palliative in recurrent surgeries, amputation as a primary treatment has not been shown to increase long-term survival compared to other treatments (21).

8. Prognosis

The 5-year survival rate of Ewing sarcoma is up to 75 in solitary lesions. Poor prognostic factors include axial skeletal location such as sacrum, pelvis or vertebra, primary lesion being larger than 10 cm at the time of diagnosis, presence of metastasis at the time of diagnosis, and progression under chemotherapy treatment (22).

Although there are studies showing that the survival of recurrent solitary metastases, even if they are pulmonary, is the same as the recurrence of the primary site, a consensus has still not been reached (23, 24).

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CHAPTER VII

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)

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1. Introduction

Post-transplant lymphoproliferative disorder (PTLD) refers to the excessive growth of B cells resulting from therapeutic immunosuppression after an organ transplant. In these individuals, the immune system is intentionally suppressed to prevent organ rejection, which can lead to certain complications. PTLD can manifest as infectious mononucleosis-like lesions or the overgrowth of a diverse population of B cells known as polyclonal polymorphic B-cell hyperplasia. Within this hyperplasia, some B cells can acquire mutations that transform them into malignant cells, ultimately leading to the development of lymphoma.

In certain cases, the malignant cell clone can become the predominant proliferating cell population, giving rise to a distinct type of lymphoma known as frank lymphoma. This specific lymphoma subtype is observed predominantly in immunosuppressed patients who have undergone organ transplantation.

According to the updated 2016 classification by the World Health Organization (WHO), post-transplant lymphoproliferative disorder (PTLD) has been further categorized into different subtypes. These include plasmacytic hyperplasia PTLD, infectious mononucleosis PTLD, florid follicular hyperplasia PTLD, polymorphic PTLD, monomorphic PTLD (B- and T-/NK-cell types), and classical Hodgkin lymphoma PTLD. Among these subtypes, diffuse large B cell lymphoma (DLBCL) is the most common type observed in PTLD cases.

While the majority of PTLD cases involve B cells, approximately 5-10% can be of T/NK-cell or Hodgkin lymphoma type. Furthermore, around 70% of PTLD cases are associated with the Epstein-Barr virus (EBV), especially when PTLD occurs shortly after transplantation. The development of PTLD is thought to be linked to EBV proliferation in the presence of long term immunosuppression, which suppresses the immune function of T cells (1-3).

There are several factors that increase the risk of developing post-transplant lymphoproliferative disorder (PTLD) following an organ transplantation. One such factor is the lack of a prior primary infection with the Epstein-Barr virus (EBV) before the transplantation procedure. Additionally, a higher level of immunosuppression and a specific type of immunosuppressive regimen can be indicative of a heightened risk for PTLD. In cases where the organ donor or recipient has an active EBV infection, it is recommended to gradually reduce the dosage of immunosuppressive medications. This approach is suggested in order to minimize the risk of PTLD (3-7).

2. Epidemiology

Post-transplant lymphoproliferative disorder (PTLD) is a rare malignancy that can develop as a complication of liver transplantation. Despite its relatively low incidence, PTLD has significant and serious consequences. Among such complications, skin cancer is the most commonly observed, while PTLD ranks as the second most frequent. Although less common, PTLD can also develop after hematopoietic stem cell transplantation. The incidence of PTLD varies depending on the type of transplantation, with lower rates observed in bone marrow and liver transplants. On the other hand, lung and heart transplants have the highest rates of PTLD due to the necessity for higher levels of immunosuppression. The occurrence of PTLD is most prevalent within the first year after transplantation, with approximately 80 percent of cases arising during this period.

The documented occurrence of PTLD ranges from 2% to 20%, with a higher prevalence observed among individuals who undergo a solid organ transplantation in comparison to those who receive an allogeneic stem cell transplant (8).

From January 2006 to December 2020, 1288 liver transplants were performed in our Liver Transplant Center. The overall incidence of PTLD in liver transplant recipients at our center was 1.08% (14/1288). The median onset of PTLD after liver transplantation was 13 months (9,10).

The risk of PTLD is further amplified in cases of bone marrow transplantation involving unmatched or mismatched HLA (human leukocyte antigen).

The main risk factors contributing to the development of PTLD include the extent of immune suppression and the presence of the Epstein-Barr virus (EBV). Specifically, higher levels of T cell immunosuppression augment the risk of PTLD. In individuals who have not been previously infected by the Epstein-Barr virus (EBV negative), receiving an organ from a donor with prior EBV infection increases the likelihood of developing PTLD by a factor of 24. Furthermore, the risk of PTLD is heightened when there is a mismatch between the CMV (cytomegalovirus) status of the donor and recipient, particularly in cases where the recipient is CMV negative and the donor is CMV positive.

3. Clinical Presentation

Post-transplant lymphoproliferative disorder (PTLD) exhibits a wide range of signs and symptoms that are diverse and not specific to the condition. Patients may experience fever, weight loss, night sweats, and fatigue, which can resemble the symptoms of infectious mononucleosis caused by the Epstein-Barr virus (EBV). Lymphadenopathy or the presence of growing tumors can lead to pain or discomfort. Dysfunction in affected organs can also occur, such as shortness of breath due to involvement of the lungs or heart. Various laboratory findings can aid in diagnosing PTLD. These include abnormally low levels of white blood cells, red blood cells, and platelets. Additionally, elevated levels of serum uric acid and lactate dehydrogenase may be observed, while serum calcium levels might be decreased. These collective findings can indicate the possibility of tumor lysis syndrome.

4. Etiology

Post-transplant lymphoproliferative disorder (PTLD) is a condition characterized by the uncontrolled growth of B cell lymphocytes that are latently infected with the Epstein-Barr virus (EBV). The production of interleukin-10, a naturally occurring cytokine involved in immune regulation, has also been implicated in the development of PTLD (11,12).

In individuals with a normal immune system, EBV can cause infectious mononucleosis in adolescents, but it usually remains asymptomatic in children during their childhood. However, in transplant patients who are immunosuppressed, the lack of T-cell immunosurveillance allows EBV-infected B lymphocytes to proliferate unchecked (13).

Immunosuppressive drugs such as tacrolimus and ciclosporin, which are commonly used in organ transplantation, inhibit the function of T cells, further impairing their ability to control the proliferation of B cells infected with EBV.

Additionally, the depletion of T cells can be achieved through the use of anti-T cell antibodies, which are employed in the prevention or treatment of transplant rejection. Antibodies such as Anti Thymocyte Globulin (ATG), Antilymphocyte globulin (ALG), and OKT3 (muromonab- cluster of differentiation 3 (CD3)) increase the risk of developing PTLD by further compromising T-cell function.

PTLD can manifest as either polyclonal or monoclonal forms. Polyclonal PTLD often presents as tumor masses, which can cause symptoms related to compression, such as bowel obstruction. In contrast, monoclonal PTLD tends to be a disseminated malignant lymphoma, spreading throughout the body.

5. Diagnosis

Histopathology is necessary to establish a conclusive diagnosis of PTLD. By conducting a biopsy on the affected tissue, pathologists can obtain a definitive diagnosis by identifying the presence of lymphoproliferative neoplasia. In most cases, the biopsy will show the presence of malignant B cells, while in a smaller number of cases, T cell neoplasia may be observed. CT imaging can detect enlarged lymph nodes or the presence of a focal mass. Additionally, a PET scan may be useful in evaluating the condition by detecting increased metabolic activity in lesions. This information can potentially guide decisions regarding the appropriate sites for biopsy.

If neurologic symptoms such as confusion or focal weakness are present, it may suggest involvement of the nervous system. In such cases, an MRI of the brain with contrast using gadolinium and a lumbar spinal tap with testing of the cerebrospinal fluid for Epstein-Barr virus (EBV) viral levels can help evaluate this possibility.

Respiratory symptoms like cough or shortness of breath, particularly in individuals with weakened immune systems, may indicate the presence of an infection. Opportunistic infections can sometimes manifest similarly to post-transplant lymphoproliferative disorder (PTLD). It is beneficial to evaluate such cases through sputum culture for bacteria, testing for Pneumocystis carinii, acid-fast bacilli, and fungal infections.

6. Management And Treatment

Post-transplant lymphoproliferative disorder has the potential to regress naturally when the dosage of immunosuppressant medication is reduced or

stopped altogether. Another treatment approach involves the administration of antiviral therapy. In certain instances, PTLD may advance to non-Hodgkin's lymphoma, posing a risk of fatality. An extensive study in the second phase revealed that the introduction of EBV-specific T cells through adoptive transfer exhibited remarkable effectiveness while causing minimal harm (14).

Consequently, treatment options for PTLD are diverse and encompass several approaches to address the underlying immune response. These include strategies aimed at reducing immune activity, employing targeted antibodies such as anti-CD20 agents, surgical interventions, radiotherapy, and chemotherapy. By employing a combination of these modalities, healthcare professionals strive to comprehensively manage and combat the condition (15-17).

7. Prognosis

The introduction of rituximab, a monoclonal anti-CD20 antibody, along with lymphoma-specific treatment regimens, has led to significant improvements in the overall prognosis for patients with post-transplant lymphoproliferative disorder (PTLD). In a multicenter, open-label trial conducted internationally, a sequential treatment approach involving rituximab followed by CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy was employed. The results showed that 89.8% of the patients responded to full or partial treatment (18).

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CHAPTER VIII

WATCH AND WAIT AND PREOPERATIVE EVALUATION OF RECTAL CANCER

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1. Introduction

Despite all the advances in rectal cancer treatment, multimodal treatment still has significant negative effects on quality of life. These are serious problems such as functional disorders of the intestine and its functioning, sexual dysfunctions, chronic pain, and the need for colostomy. For this reason, strategies that recommend less use of radiotherapy, chemotherapy and even surgery have gained importance today, and a search for reducing the toxicity of the treatment has come to the fore.

Surgery still remains the standard treatment for patients diagnosed with non-metastatic rectal cancer. Pathological complete response is observed in 10 - 20% of patients after long-term chemoradiotherapy. Therefore, an increasing number of studies are using the “watch and wait” method in carefully selected patients with rectal cancer who have a complete clinical response to chemoradiotherapy. In this method, preoperative chemoradiotherapy is applied over a period of 5-6 weeks, with a 6-10 weeks treatment break before surgery. Particularly long period of time here allows the tumor to regress.

Tumor regression is known to be an important prognostic indicator. Reducing tumor volume, reducing its stage and reducing nodal involvement are

achieved, the degree of response is then defined. There are some rating systems for this. (table1)

TRG	MANDARD	DWORAK	RÖDEL	RYAN	CAP
0		No regression	No regression		PCR
1	No residual cancer	Dominant tumor mass	Fibrosis < %25	PCR	Few tumor cells
2	Rare cancer	Dominant fibrosis	Fibrosis % 25-50	Dominant fibrosis	Dominant fibrosis
3	Fibrosis > residuel cancer	Few tumor cells	Fibrosis > 50%	Significant cancer	Dominant tumor mass
4	Residual cancer > fibrosis	PCR	PCR		
5	No regression				

Table 1: Tumor Regression Grading Systems

After chemoradiotherapy, endoscopy reveals scarring or normal mucosa at the tumor location in approximately 50% of patients. This is called clinical complete response (cCR). Pathological complete or near-complete response is observed in 10-40% of patients. Pathological complete response (pCR) means there are no residual tumor cells. In a near-complete response, single cells or small groups of cells are seen. Pathological complete response may not be observed in patients with clinical complete response.

First, in 2004, Habr Gama and colleagues reported the results of the non-surgical method in selected patients who achieved clinical complete response after chemoradiotherapy. Following HabrGama's study, other researchers reported a much higher failure rate (50-60%) than the 3% failure rate reported by Habr-Gama. Factors such as differences in tumor burden, patient selection following neoadjuvant treatment, evaluation method, timing and neoadjuvant treatment regimen may be shown as reasons for the discrepancy in these rates. In Habr-Gama's study, patients who were initially selected for nonoperative treatment and then experienced recurrence within the first 12 months were excluded from the analysis. This situation may have caused the failure rate to decrease. Current data, including Habr-Gama's latest report, indicate that the risk of local treatment failure is approximately 30%. While it is thought that a pathological complete response has developed in these patients, there are actually undetectable tumor cells. This is one of the biggest difficulties of the "watch and wait" approach. During the follow-up period in patients undergoing

"watch and wait" aprroach, CEA level should be tested every 3 months, frequent digital rectal and endoluminal examinations, and MRI evaluation should be performed when necessary. Biopsy must be absolutely performed on suspicious lesions.

Tumor recurrence is usually detected within 12-24 months. In this case, the patient is generally suitable for curative resection. However, with longer delays, salvage resection may become more difficult. The chance of sphincter-sparing surgery being performed in these patients is less than 50%.

Whether leaving residual tumor tissue in patients with cCR but not pCR, increases the risk of distant failure is still unclear. Despite this, there is increasing evidence supporting the watch and wait prosedure. Prospective series related to the watch and wait procedure are shown in the table. (Table 2)

SERİES	Number of patients (total)	Number of patients operated	Median follow-up (months)	cCR	Local regrowth	Outcome
Maas 2011 (1)	21	20	15 (observed) 35 (operated)	100%	1 patient	2-year OS 100% 2-year DFS 89%
Dalton 2012 (2)	12	37	25.5 (mean)	24%	50%	Disease free at follow-up
Habr-Gama 2014 (3)	93	90	60	49%	31%	5-year OS 91% 5-year LRFS 69% 5-year DFS 68%
Smith 2015 (4)	73	72			26%	4-year OS 91% (obs) vs. 95% (surg) 4-year DSS 91% (obs) vs. 96% (surg)
Smith 2015	18	30	68.4 (mean)		1 patient	Alive with pelvic disease at 54 months

Table 2: Watch and wait current studies

2. Clinical Evaluation Of Treatment Response

Clinical evaluation of treatment response is the biggest challenge in applying the watch and wait method. Considering the concordance between clinical and pathological assessment, the sensitivity for detecting pCR is approximately 25% and the specificity is 60-90%.

There is no definitive method for clinical assessment of complete response. However, rectal examination and endoluminal examination must be performed to detect residual mass, ulceration, nodularity or stenosis. Regular and smooth mucosa, whitening or telangiectasis must be observed to be able to say that there is a clinically complete response. Some authors advocate local excision

of the tumor bed. Full-thickness excision can be performed by methods such as transanal excision, trans-anal endoscopic microsurgery (TEM), or trans-anal minimally invasive surgery (TAMIS).

PET and MRI are the recommended radiological evaluation methods to determine the treatment response. PET is not reliable in evaluating patients with complete response. MRI is the best imaging method to determine the response in the "watch and wait" method.

In the MERCURY (5) study, tumor regression grade was established. (Table 3). It was found that the survival of patients with mrTRG 1-3 was better than that of mrTRG 4-5.

MR Tumor Regresssion Grade	Definition
1	Low signaling fibrosis
2	Minimal residual tumor
3	Intermediate intensity tumor signal
4	Minimal fibrosis
5	No change from baseline

Table 3: MRI tumor regression rate.

The following methods have been tried to increase the PCR rate and apply the watch and wait method:

- Intensification of radiotherapy
- Use of more effective chemotherapeutic agents
- Induction and consolidation chemotherapy
- Extending the time from chemoradiotherapy to surgery

More research is needed for the watch and wait method to be put into routine use. Currently, this method should only be offered to patients as an option in the context of clinical research.

3. Preoperative Evaluation Of Rectal Cancer

The first stage of evaluation begins with a general physical examination, especially a rectal examination in patients with known symptoms of rectal cancer (such as change in bowel habits, bleeding, abdominal pain, tenesmus) or with known clinically suspicious anamnesis. The location of the tumor (distance from the anal verge, proximity to the anal sphincter and pelvic floor) and texture

(soft, hard, mobile) not only help diagnosis, but also provide information about the stage or histology of the tumor. Preoperative examinations can be classified as endoscopy, imaging and laboratory examinations.

3.1 Anamnesis

- Previous medical and surgical history (especially previous intestinal surgery is important to determine the gastrointestinal system anatomy)
- History of the family
- Comorbidities/drugs

3.2 Symtpoms

Duration and severity
-Changes in bowel habits
-Rectal bleeding
-Abdominal pain/swelling
-Tenesmus
-Unexplained anemia
-Loss of weight/appetite

3.3 Physical Examination

-Rectal examination: The location, texture, size and fixation of the tumor. Additional anorectal diseases.
- General system examination

3.4 Endoscopy

-Anoscopy/Proctoscopy
-Flexible sigmoidoscopy
-Colonoscopy
-Capsule endoscopy

3.5 Imaging

-Plain abdominal radiography: intraabdominal free air
-Computed Tomography
-Magnetic Resonance
-PET
-Endorectal ultrasonography

3.6 Laboratory

-Complete blood count
-Biochemical analysis of blood
-Fecal occult blood test
-Fecal immunochemical test
-CEA (increased in 60-90% of patients)
-Genetic testing

The 60 cm flexible fiberoptic sigmoidoscopy reaches from the rectum to the splenic flexure allowing lesions to be visualized and biopsy samples to be taken. The disadvantages of flexible sigmoidoscopy are that it only allows examination of the distal part of the colon and biopsy samples cannot be taken from a sufficient depth (at least 40 cm). Advantages are that bowel preparation is less intensive than colonoscopy and it requires less sedation. It is used as a screening test especially in patient groups at risk for colorectal cancer (such as familial adenomatous polyposis, Lynch II syndrome).

Colonoscopy evaluates the entire colon, rectum and the end of the ileum. It is used to confirm and exclude synchronous lesions in all patients with rectal cancer and is the most frequently used examination in the diagnosis of colorectal cancers in order to determine the histopathology of the tumor through biopsy. Although it has disadvantages such as requiring bowel preparation and diet, being performed under sedation, and having more complications, it is still considered as the gold standard today. In Colon Capsule Endoscopy, the patient swallows a capsule containing small wireless video cameras that capture images as it passes through the colon. Colon capsule endoscopy is approved by the U.S. Food and Drug Administration (FDA) for use only in patients whose colonoscopy has not been completed, not as a stand-alone screening option.

Endorectal Ultrasonography (ERUS) is primarily used to evaluate the depth of invasion of neoplastic lesions in the rectum. The normal rectal wall appears as a five-layered structure. Ultrasonography can safely differentiate many benign polyps from invasive tumors by determining whether the integrity of the submucosal layer is preserved. Also superficial (T1-T2) tumors and deep (T3-T4) tumors are distinguished. It has also proven to be useful in the early detection of local recurrence of cancers after surgery. Malignant lymph nodes appear as hypoechoic and rounded peritumoral structures, whereas benign lymph nodes appear isoechoic with perirectal fat. High-resolution MRI is particularly sensitive in showing the extension of rectal tumors to the pelvic

sidewall. It precisely determines the invasion of the tumor into the mesorectum. It is increasingly used in preoperative evaluation due to its increased ability to evaluate the surgical resection margin at risk. ** The use of intravenous contrast is controversial; the addition of contrast did not improve tumor or nodal staging by MRI in three separate studies (6-8), other studies have shown that evaluation of abnormal contrast enhancement patterns in lymph nodes may add diagnostic value. PET is a nuclear medicine imaging that uses the excess rate of glycolysis in tumor cells to detect tumor.. F-fluorodeoxyglucose (FDG) is the marker. It is especially used in the following situations: in the detection of metastasis / if there is a suspicious finding on CT / In the presence of local recurrence in the pelvis

3.7 Staging

Preoperative staging is performed according to the TNM classification of malignant tumors by estimating the depth of invasion into the rectal wall (cT), the presence or absence of lymph node metastasis (cN) and the presence of distant metastasis (cM). T stage, The T stage of rectal cancer is determined by the depth of spread of the primary tumor, including the involvement of adjacent anatomical structures. Tis tumors are limited by the mucosa. T1 tumors confined the submucosa without affecting the muscularis propria. T2 tumors invade the muscularis propria but do not extend beyond it, while T3 tumors extend along the muscularis propria into the subserosa or perirectal fatty tissue. T4a tumors invade a serosal equivalent layer (typically peritoneum or mesorectal fascia), and T4b tumors invade another organ (e.g., pelvic floor muscles, prostate or vagina).

cT1-2 tumors, All patients with T1-2 invasive rectal cancer arising from a polyp should undergo local staging (MRI or TRUS) to determine the primary tumor stage and evaluate lymph node positivity.

Distnction between T2 and T3 Making the distinction between a T2 tumor involving the muscularis propria and a T3 tumor that invades beyond the muscularis propria is very important as it will change the direction of treatment (preoperative radiotherapy or chemoradiotherapy). The presence of a large tumor in the perirectal fat tissue immediately indicates that the tumor is T3, but the difference between an advanced T2 tumor and a very early T3 tumor can be very small so this distinction can be difficult to make. Locally advanced rectal cancers can invade surrounding organs. The most common sites of invasion are the prostate, urethra, urinary sphincter complex, seminal vesicles, vagina and pelvis.

Distinction between T3 and T4a The distinction between a clinical T3 and T4a tumor in the rectum requires careful evaluation of the position of the peritoneal surfaces of the rectum relative to the site of tumor involvement. For rectal cancers below the level of the peritoneal reflection (typically at the level of the seminal vesicles or vaginal fornix), the tumor within the mesorectal fat is evidence of T3 disease and in order to be considered as a T4 lesion the tumor must extend into the mesorectal fascia. However, the front surface of the rectum is covered with serosa (peritoneum) and is above the peritoneal reflection. This lining extends laterally around the rectum as we progress upward into the sigmoid colon. This layer is usually not visible on imaging, so its location must be estimated based on regional anatomy. In men, this reflection is typically located at the level of the seminal vesicles. In women, this reflection is located near the posterior edge of the vagina. For tumors extending above the peritoneal reflection, the presence of large tumor in the pericolonic fat represents T4a disease if present on a serosal coated surface and T3 disease if present on an uncoated surface.

NX	Regional lymph nodes cannot be evaluated
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive (tumor in lymph nodes is ≥0.2 mm) or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the following areas: -Subserosa -Mesentery -Non peritonealized pericolic or perirectal/mesorectal tissues
N2	Four or more regional nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive

Table 4 : N Staging

M0	No distant metastasis proven by imaging or similar; no evidence of tumor in distant sites or organs. (This category is not assigned by pathologists.)
M1	Metastases to one or more distant sites or organs or peritoneal metastases are identified
M1a	Metastasis to a site or organ is defined without peritoneal metastasis
M1b	Identification of metastases to two or more sites or organs without peritoneal metastases
M1c	Metastasis to the peritoneal surface is defined alone or in combination with metastases from other regions or organs.

Table 5: M Staging

4. Result

The watch and wait approach can only be recommended to patients as a clinical study, and preoperative evaluation should be done very carefully.

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CHAPTER IX

PEDIATRIC SYNOVIAL SARCOMA

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1. Introduction

Synovial sarcoma (SS) a very rare tumor detected in children where epithelial differentiation is observed. (1,2) The incidence of synovial sarcoma is 2-3 per 100,000. (3) SS is one of the types of Soft Tissue Sarcomas (STSs) and constitutes 5-10% of STSs. (4) It can occur at any age and can arise in any part of the body. The tumor's behavior and histology can also vary. (5) In SS, the (X;18)(p11.2;q11.2) translocation is observed. (6) SS is commonly encountered in the lower extremities (60%), upper extremities (23%), head-neck (9%), and retropharyngeal regions. (7,8) Prognostic factors include age, location of detection, size, percentage of necrosis, mitotic activity, and neurovascular invasion. (9) The prognosis of Synovial Sarcoma is better in children compared to adolescents. Although clinical, radiological, and histological findings may be similar, the 5-year overall survival (OS) is higher in children than in adolescents. (10) Although SS is sensitive to chemotherapy, it has a tendency to develop recurrence and metastasis. (11) The most common site of metastasis is the lungs. (12) If metastasis is detected, the patient's chances of survival are very low. (13)

2. General Information

2.1. Definition

SS is a type of STS that exhibits both mesenchymal and epithelial differentiation. (14) SS is a rare, malignant tumor that often occurs in the tissues surrounding the joints. Diagnosing and treating this type of cancer can be challenging. (15)

2.2. Epidemiology

SS constitutes approximately 10% of all STSs. (16) The incidence of synovial sarcoma is 2-3 per 100,000. (3) SS typically occurs in adolescents. (17)

2.3. Pathogenesis

The pathogenesis of SS is still not fully understood. Genetic mutations may play a significant role in the development of SS. Specifically, it has been shown that genetic fusions such as SYT-SSX1 or SYT-SSX2 are effective in the formation of this type of cancer. These fusions can disrupt normal cell growth and division control, thereby promoting the formation of cancer. (18,19)

2.4. Etiology

The epidemiological data regarding SS is insufficient. (20) SS is thought to arise from multipotent mesenchymal cell (MSC). (21)

2.5. Pathology

SS is a malignant STS. There are 3 types of SS: biphasic, monophasic, and poorly differentiated. (22) Biphasic SS is composed of spindle and epithelioid cells, while monophasic SS is made up of a single cell type. (23) Poorly differentiated SS, refers to a variant where tumor cells are less differentiated or more primitive. Less differentiated cells can imply that the tumor is more aggressive or can grow more rapidly. (24) SS often shows positive responses to the epithelial markers EMA, cytokeratin (CK 7, CK 19), vimentin, CD 99, and BCL-2. (25)

2.6. Genetic

SS is a malignancy driven by the SS18-SSX fusion. (26) It has been reported that SS is suppressed by cytokines secreted by macrophages and T cells. (27)

2.7. Clinical Findings

SS is a malignancy with slow growth that presents with atypical symptoms lasting for approximately 2 years. (28) Due to its insidious onset, occurrence in adolescents, and atypical initial symptoms, these patients can initially be clinically mistaken for benign conditions such as myositis, synovitis, or tendinitis. (29) It often follows an asymptomatic course. Symptoms such as dysphagia, dyspnea, and pain have been reported. (30)

2.8. Diagnosis

The diagnosis of SS involves a medical history, physical examination, radiological imaging, biopsy, pathological examination, immunohistochemistry, and molecular tests. (31) Magnetic resonance imaging (MRI) is an imaging method used to define the size of the tumor preoperatively. (32) The detection of SS18-SSX is crucial in making the diagnosis. (33)

2.9. Management

The treatment for SS is wide local tumor resection. Adjuvant radiotherapy and chemotherapy may be applied to reduce the recurrence rate. (34) It is known that synovial sarcoma exhibits a high rate of local recurrence and metastasis even after remission. Therefore, close monitoring is necessary for patients who have achieved remission. (35)

3. Conclusion

The rarity of SS underscores the need for multinational prospective studies in children and adolescents to develop appropriate approaches.

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CHAPTER X

ESOPHAGIAL CANCER SURGERY AND APRROACH TO COMPLICATIONS

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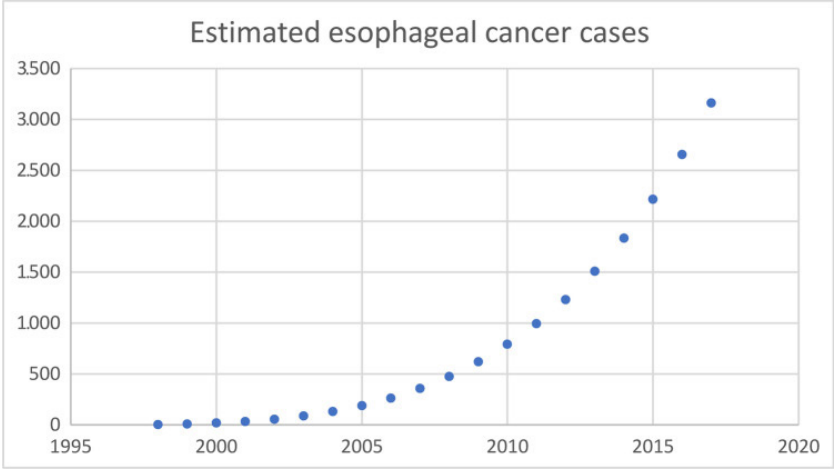
1. Esophaegal Cancer

Esophageal cancer remains an integral cause of cancer-related death and has shown a drastic increase of more than 6-fold in incidence rates worldwide. Esophageal cancer is often diagnosed during



its advanced stages. 5-year postesophagectomy survival rates (15-40%) There are two histological type worldwide: squamous cell carcinoma and adenokarsinoma.(1)

1.1. Risk factors for squamous carcinoma: Gender and race, smoking, alcohol, diet and nutrients, genetics

1.2. Risk factors for adenokarsinoma: Gender and race, gastroesophageal reflux disease and barrett's esophagus,obesity

2. Early Diagnosis And Screening of Esophageal Carcinom

Endoscopy is the gold standard for the diagnosis of pre-cancerous squamous lesions. The sensitivity 62% and specificity79% of white-light endoscopy for the detection of high-grade dysplasia and cancer. (3)

Transthoracic and transhiatal esophagectomy for benign and malignant diseases of the esophagus is associated with a high rate of morbidity and mortality. In the present study, we aim to analyze the esophagectomy procedures and evaluate the causes of mortality and morbidity.

Morbidity rates after esophagectomy are approximately 50% and operative mortality rates are around 10%. Choosing the most appropriate surgical procedure, the patient, and good preoperative preparation of the patient are important in such cases. We believe that early diagnosis of potential complications and effective treatment of these complications can reduce the significant morbidity and mortality rates in esophagectomy procedures.

3. Esophagectomy

Esophagectomy is currently a successful surgical procedure for both malignant and benign esophageal diseases. The most common methods are transhiatal esophagectomy and transthoracic, or Ivor Lewis esophagectomy. However, there is a significant risk of morbidity and mortality after these procedures. As a result, the selection of eligible candidates and the effective treatment of potential complications increase the quality of life.

Despite improvements in patient selection, surgical technique, and intensive care facilities, operative morbidity, and mortality rates after esophagectomy remain significantly high . While morbidity and mortality have tended to decrease in the last three decades with early diagnosis and effective treatment of complications, a recent survey study on esophagectomy reported a mean

major morbidity rate of 52%. In a prospective cohort study of 17395 patients by Connors et al., morbidity and mortality rates were also reported as 50.7% and 8.8%, respectively.(4)

Respiratory failure is one of the most common causes of mortality, with a rate of approximately 13% observed in studies **.** It is recommended that patients should be followed up on a ventilator for the first 24-48 hours due to impaired respiratory function in the postoperative period and weakness of respiratory muscles after thoracotomy. It is also emphasized that postoperative respiratory physiotherapy must be performed. It has also been reported that oral hygiene should be prioritized to reduce pneumonia after aspiration **(5)**. In our clinic, we meticulously examine the cardiopulmonary status of all preoperative resection cases and provide postoperative respiratory exercise and perioperative oral care following smoking cessation.

The use of appropriate operative techniques is another important step in lowering the rate of postoperative complications. Transhiatal and transthoracic approaches are the methods used in esophagectomy. Thoracotomy allows for good exposure and direct dissection of tumors from mediastinal structures in the middle and upper thoracic lesions **.** Transhiatal resections are used for resections in the distal esophagus and gastroesophageal junction**.** In their series of benign and malignant diseases, Orringer et al. recommended the transhiatal approach regardless of tumor localization **(6,7,8)**. Some studies have also found that transhiatal procedures have lower rates of pulmonary complications and mortality than transthoracic procedures. However, Kari et al. showed that the complication rates of the transthoracic approach were acceptable **.** Studies have also shown similar postoperative results in both groups

The choice of surgical method is important in terms of postoperative morbidity and mortality. The potential advantages of transhiatal resection are that it is less invasive and can be performed rapidly. The absence of a thoracotomy results in less postoperative pain, fewer pulmonary complications, and faster recovery. Dissection is performed under direct visualization in the transthoracic approach, so injuries to the tracheobronchial tree, azygos vein, and ductus thoracicus are less likely. Another advantage of transthoracic esophagectomy is that it allows mediastinum and paraoesophageal lymphatic dissection. Two large meta-analyses reported that transthoracic interventions resulted in higher perioperative morbidity and mortality rates, but there was no significant difference in long-term survival between the two methods **.** A comparative study with the highest number of cases compared 114 cases of

transthoracic intervention with 106 cases of transhiatal intervention. The transthoracic group had a higher rate of pulmonary complications, ventilation time, intensive care unit stay, and hospitalization duration. No difference was found between the groups in terms of hospital mortality. The 5-year survival and life expectancy were 39% and 40% in the transthoracic group and 27% and 29% in the transhiatal group, respectively **(9,10,11).**

Transhiatal esophagectomy seems inappropriate for middle and upper 1/3 thoracic tumors and tumors closely related to tracheobronchial tissues. The neoadjuvant treatment makes transhiatal intervention dangerous. Therefore, for lesions in the supracarineal and mid-thoracic esophagus, a transthoracic approach was recommended, while a transhiatal approach was recommended for cancers in the distal esophagus, particularly in the cardioesophageal region. Surgeons performing transhiatal esophagectomy should be aware that this procedure includes a limited lymph dissection. Transhiatal esophagectomy is therefore recommended in benign lesions [perforation] where lymphatic dissection is not required, Barrett's esophagus with high-grade dysplasia, and Siewert type and III tumors involving the junction. We performed transthoracic esophagectomy in 8% of the cases in our series. The multicentric localization of esophageal cancers, wider lymphatic dissection, and improved survival all play a role in our decision to use this method.

Anastomotic leakage is a major complication after esophagectomy and can be fatal. Poor blood supply to the esophagus has been said to increase the risk of anastomotic leakage, but it has also been said that poor blood supply to the esophagus does not cause problems and that blood supply will be sufficient even if the esophagus is significantly mobilized. The prevalence has been reported to be approximately 3.5-13% in series**.** It has been stated that preventing ischemia in anastomosis and paying attention to anastomosis techniques can reduce these rates**.** The use of a linear stapler significantly reduces the risk of anastomotic leakage, and stricture formation is not observed **(12,13,14).**

While some studies suggest that early reoperation should be performed in case of anastomotic leakage , some studies suggest that the operation should be selective, and non-operative follow-up may be beneficial . The anastomoses in the esophagectomies in this study were performed with the linear stapler and anastomotic leakage developed in only three patients [18%]. Linda et al. reported that mortality did not occur in patients who developed leakage following esophagectomy and intrathoracic anastomosis, with reoperation and

reinforcement suture placement as needed **(15,16,17).** The mucosa and submucosa [M-SM] are retracted during esophageal incision. We therefore recommend M-SM during suture placement to reduce the risk of esophagogastrostomy or jejunostomy leakage. We believe that preservation of the gastric fundus is important in anastomoses in the neck. This makes it possible to create a longer segment. It is important that the stomach does not rotate during the withdrawal to the neck or the chest wall.

Dopamine infusion is recommended if required to prevent hypotension and low cardiac output. Cervical esophagogastric leakage is reported in 10% of cases. The hospitalization duration is prolonged. It occurs in 5-8 days and may leak from the drain or incision. Cervical emphysema and redness develop. If the skin is reddened, crepitated and there is discharge, the wound should be opened again and irrigated. It can be performed at the bedside or in the operating room. In rare cases, the leakage does not resolve and may flow into the mediastinum, resulting in a septic picture and mortality.

Esophageal stricture is a common problem after esophagectomy. This condition lowers the quality of life. Stricture development is influenced by surgical techniques used during stomach preparation, placement, and anastomosis. It is not advised to use staples numbered 21-25. It is usually relieved by dilatation and rarely requires reoperation.

Transhiatal approach is mostly preferred in benign esophageal disease resections and complication rates have been reported to be lower than in malignant diseases**.** The reasons for this include the fact that weight loss in patients with benign esophageal disease is usually less pronounced than in patients with malignant esophageal disease and that malignant diseases necessitate more radical dissection to ensure clear surgical margins. In patients requiring perforation resection, aggressive mediastinal debridement is recommended **(18, 19, 20).**

4.Conclusion

Esophagectomy can be performed effectively in the treatment of both benign and malignant esophageal diseases. Choosing the most appropriate surgical procedure, the patient, and good preoperative preparation of the patient are important in such cases. We believe that early diagnosis of potential complications and effective treatment of these complications can reduce the significant morbidity and mortality rates in esophagectomy procedures.

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