Chapter 15
Point-of-Care Clinical Guide: Gallbladder Cancer

Abdulrahman Y. Hammad, Natesh Shivakumar, and T. Clark Gamblin

Patient's Perspective: Questions on Gallbladder Cancer

What Are the Main Risk Factors for Gallbladder Cancer? Is My Family at Increased Risk?

Gallbladder cancer affects women more than men with a ratio of 3:1. The disease has a geographical distribution with very high rates in Bolivia, Chili, Ecuador, followed by Asian countries such as China and Japan.

There is a strong association between gallstones and gallbladder cancer. Gallstones are present in up to 75 % of people affected with gallbladder cancer. Porcelain gallbladder and large adenomatous polyps signify higher risk. A higher incidence of gallbladder cancer is also present in patients with gallbladder infections such as typhoid bacillus.

A.Y. Hammad, M.D. • N. Shivakumar
• T.C. Gamblin, M.D., M.S. (✉)
Division of Surgical Oncology, Medical College of Wisconsin, 9200 West Wisconsin Avenue, Milwaukee, WI 53226-3596, USA
e-mail: tcgamblin@mcw.edu

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There is an increased risk of GC among first degree relatives with studies showing a relative risk of 4.8 (95 % CI: 2.4–8.5). However, gall bladder cancer is such a rare cancer the overall risk that family members will be affected is still very low.

I Was Diagnosed with a Stage II Disease, What Are My Options? Will I Need to Receive Chemotherapy or Radiation After My Surgery for Gallbladder Cancer?

Surgical resection represents the core of gallbladder cancer management. Patients with stage II disease typically receive a laparoscopic evaluation of their disease followed by the removal of their gallbladder, gallbladder bed, and a part of the adjacent liver tissue. Clear resection margins signify a more successful operation, with a higher chance of survival.

Generally radiation and chemotherapy are not used post-operatively for gallbladder cancer. Scarce reports show that radiotherapy may provide benefit for patients with stage≥2. As for chemotherapy, there is no evidence to support its delivery following a successful operation. However, chemotherapy can be used for those with advanced diseases as evidence suggests that a combination of gemcitabine and cisplatin provides a survival advantage.

Gall Bladder Cancer and Cholangiocarcinoma

Overview

Gallbladder cancer is an uncommon disease that carries a high mortality rate due to its often late presentation. The disease follows a slow steady asymptomatic growth, and may be discovered incidentally at an earlier stage during a cholecystectomy. Gallbladder cancer possesses an infiltrating growth pattern towards the neighboring portal vasculature.

Historically, in 1924 Alfred Blalock stated that "no operation should be performed" following the diagnosis of gallbladder cancer, as surgery will only shorten the patient's life [1]. This nihilistic view was carried for years due to patients' limited survival. Recent studies report a decline in mortality rates in several parts of the world, although survival remains dismal for advanced stages. Gallbladder cancer is more commonly seen in South American countries such as Chile, Bolivia, and Ecuador, followed by Eastern Asian Countries such as Japan and South Korea. Lower incidence of the disease is reported in Europe; and the North American continent is considered a low risk area. No clear factors are associated with the development of gallbladder cancer; yet some risk factors are frequently linked to it. In the next sections, possible risk factors are discussed followed by clinical presentation, investigations, and treatment considerations for patients with gallbladder cancer.

Epidemiology

Gallbladder cancer (GBC) is the most common biliary tract neoplasm and the fourth most common upper gastrointestinal malignancy worldwide. The disease shows a predilection for females older than 65 years [2, 3]. The female–male (F/M) ratio of the disease varies worldwide and is typically around 2.5/1. Higher F/M ratios exist in countries with high risk such as Pakistan, Columbia, and Spain, while countries such as Japan, Korea, and China approach a 1:1 ratio.

Worldwide, the highest incidence of GBC is reported in Bolivia and Chile (15/100,000), followed by eastern Asian countries such as South Korea, and Japan. Eastern European countries exhibit intermediate incidence rates, while lower rates (<3/100,000) are reported in the US, the UK, and New Zealand. Reports show different incidence rates in ethnic groups, suggesting a possible contribution of ethnicity towards the risk of disease [4].

In the US, the incidence of the disease is lower than other parts of the world. A previous analysis of the Surveillance,

Epidemiology and End Results (SEER) database revealed an overall incidence of 1–2 cases/100,000 [5]. The Caucasian population exhibit a 50 % increased likelihood of diagnosis compared to the African American population. Hispanic women in California and New Mexico has the highest incidence among all US ethnic groups (8.2/100,000 and 5.4/100,000, respectively) [4]. Subsequent reports show a decline in the incidence of the disease that is more noticeable in American Indians followed by Hispanics and non-Hispanics [6].

Analysis of mortality trends worldwide indicated minimal mortality changes in countries with low risk of the disease, such as Spain and Italy, although other countries such as Australia, Canada, and the UK displayed a declining mortality rate. Countries with high risk of the disease, such as Chile or Japan, have experienced an increase in GBC mortality [3]. In the USA, a decrease in cancer-related mortality was seen for the period between 1980 and 1995 [3].

Nihilism associated with gallbladder cancer has recently begun to change. An analysis of the SEER demonstrated a median survival of 19 months for patients with stage I disease, 7 months for stage II, 4 months for stage III and 2 months for patients presenting with stage IV disease, representing an improvement from previous reports [7, 8]. The wide geographical and ethnic variability associated with gallbladder cancer suggests multifactorial causes and is the focus of future strategies.

Etiology

Cholelithiasis (Gallstones)

Gallstones are an established risk factor for gallbladder cancer, and up to 90 % of patients with GBC have a history of gallstones [9–11]. Previous studies reported signs of epithelial hyperplasia, atypical hyperplasia and carcinoma in situ in cholecystectomy specimens of patients having a history

of cholelithiasis [12]. Patients with gallstones carry a relative risk (RR) of 3.6–4.4 for GBC [4, 13]. A positive correlation exists between the size of gall stones and the cancer risk. Patients with stones ≥3 cm have a 9.2–10.1 RR of GBC compared to those with stones <3 cm [14, 15].

Larger stones are associated with epithelial inflammation of greater duration and intensity, and may promote dysplasia, inducing carcinoma [3]. Furthermore, the bacterial breakdown of some bile components and the subsequent production of endogenous carcinogen may add to the inflammatory process [3]. This theory is challenged by the fact that only a minority of patients with gallstones actually develop cancer (1–3 %), suggesting that other genetic and environmental risk factors contribute [16, 17].

Porcelain Gallbladder

Gallbladder wall calcification may occur as a consequence of long standing inflammation. The term "porcelain gallbladder" refers to the pathological presence of widespread calcifications, in association with discoloration and brittle consistency of the gallbladder wall [18]. The disease is associated with cholelithiasis in more than 95 % of the case and is more prevalent starting in the sixth decade of life, with a female predominance (female to male ratio of 3–5:1) [19, 20]. The condition is typically asymptomatic and is often diagnosed incidentally on abdominal imaging or following the discovery of a palpable right upper quadrant abdominal mass. Recent studies report cancer development in 15 % of the cases; a lower incidence compared to previous reports [21, 22]. The different incidences may be due to different ethnic populations studied [23]. Yet the causality relationship between porcelain gallbladder and gallbladder cancer remains unproven. Prophylactic laparoscopic cholecystectomy for this pathology is not mandatory and remains debated [22, 24, 25].

Polyps

Gallbladder polyps represent mucosal outgrowth and can be benign or malignant. Benign gallbladder polyps include adenomas, adenomyomas, inflammatory polyps and cholesterol polyps. Cholesterol is the most common type of polyps, accounting for more than 50 % of all identified [26]. Adenocarcinoma compromises most of the malignant polyps; in addition to less frequent squamous cell carcinoma, angiosarcoma, clear cell cancer, and metastatic disease. Several studies have investigated the association between size, shape (sessile vs. pedunculated), number of polyps, and gallbladder cancer. Typically, polyp size >10 mm and sessile morphology in ages >50 years represent a high risk with malignancy [27, 28]. Endoscopic ultrasound (EUS) and computed tomography (CT) can differentiate benign from malignant polypoid lesion with high sensitivity [29, 30]. Transabdominal ultrasound is reported as a superior imaging modality compared to EUS in differentiating smaller neoplastic versus non-neoplastic lesions [31]. At present, it is widely acceptable that patients with a polyp ≤10 mm can be safely observed while those >10 mm should be considered for cholecystectomy due to malignancy risk [32–36].

Anomalous Pancreaticobiliary Duct Junction

Anomalous pancreaticobiliary duct junction (APBDJ) is an abnormal anatomic variation of the pancreatic duct and the common bile duct, resulting from embryologic ducts migration failure. This anomaly occurs outside the duodenal wall and results in the formation of a long common channel (usually longer than 15 mm). The shared channel prior to the duodenal wall is not controlled by the sphincter of Oddi, and thus leads to free flow of pancreatic juice into the bile tract. Subsequent activation of proteolytic enzymes, inflammation and bile stasis may lead to precancerous changes in the gallbladder mucosa. The condition is most prevalent in the Asian population and in females and is reported in 4.6–12.9 % of

GBC patients [37–41]. Hu et al. reported a strong association of APBDJ with GBC (odds ratio: 50.7, $p<0.001$). Due to the high frequency of malignancy reported in patients with APBDJ, prophylactic cholecystectomy is considered [38, 42].

Carcinogens

Different carcinogens are suggested as causal agents of gallbladder cancer. Increased risk has been reported in workers of oil, paper, chemical, shoe, textile, and cellulose acetate plants. Miners exposed to radon also carry a higher risk, signifying another potential occupational hazard [3]. Exposure to wood or coal dust has also been proposed as independent risk factors for gallbladder cancer [43]. Furthermore, some studies report that gallbladder cancer is more prevalent in smokers [44, 45]. A dose-dependent relationship exists between smoking and gallbladder cancer, although the mechanism by which smoking affects the gallbladder is unknown.

Other Factors

Possible associations also exist between typhoid infection and gallbladder cancer [16, 46, 47]. Eradication of the carrier state and elective cholecystectomy has been suggested as possible management strategies for patients with typhoid [48, 49]. Other studies examining the association of some drugs and biliary tract cancer suggested that methyl dopa, and isoniazid might also represent risk factor in cancer pathogenesis [50–52].

Clinical Presentation

Patients with GBC tend to present with one of four different clinical presentations; (1) GBC suspected based on symptoms, (2) GBC discovered incidentally on abdominal imaging, (3) GBC discovered intraoperatively during cholecystectomy, or lastly (4) GBC discovered on pathological examination of a cholecystectomy specimen. The disease

is most commonly discovered intra- and/or post-operatively on pathological examination of surgical specimens. In a study examining 435 gallbladder cancer cases from Memorial Sloan Kettering Cancer Center, 47 % of all cases were discovered incidentally during a laparoscopic cholecystectomy [53]. In general, GBC is reported in 0.27–2.1 % of all laparoscopic cholecystectomy cases [25, 54, 55]. This mode of presentation stresses the importance of surgeon-directed mucosal examination of the gallbladder specimens following cholecystectomy and frozen section examination for any suspicious lesion [56, 57].

Patients with GBC tend to remain asymptomatic in the earlier stages, and thus often present at an advanced stage. However, symptoms, if present, are usually nonspecific and their presence for an extended period of time should raise suspicion of GBC. Symptom wise, pain is reported as the most common complaint in GBC patients, followed by weight loss, anorexia, nausea, and vomiting [58]. If jaundice is the presenting sign, it signifies the presence of advanced disease that is often unresectable [59, 60]. Similarly, the presence of a palpable mass in the RUQ may predict an advanced unresectable gallbladder malignancy [61].

Investigations

Ultrasound: Ultrasound is typically the first imaging modality in the gallbladder examination due to its high availability, low cost and easy handling. Intraluminal growths and suspicious polyps can often be detected by ultrasound. Identification of asymmetric thickening of the gallbladder wall and mucosal irregularity are also possible [62]. Ultrasound can additionally detect the presence of a mass lesion replacing the gallbladder or invading the gallbladder bed at the interface with the liver. Findings that increase the likelihood of GBC include gallbladder wall calcifications (porcelain gallbladder), mural thickening, and large gallbladder stones. Color sonography may further facilitate the process by showing an

increased blood flow velocity within gallbladder lesions, which is associated with GBC [63, 64]. Overall, ultrasound is valuable in diagnosing gallbladder cancer; however, its ability to identify nodal involvement or peritoneal metastasis is limited, making it less useful in disease staging [65–68]. Ultrasound is also limited by the body habitus of the patient and is also operator dependent.

Endoscopic ultrasound (EUS) has been proposed as a possible adjunct imaging for further evaluation of suspicious lesions [65]. Findings such as gallbladder wall thickening beyond 10 mm, disruption of the normal two-layered gallbladder wall and hypoechoic internal echogenicity are independent predictors of GBC [69, 70]. EUS is useful in investigating the depth of gallbladder wall invasion, T-stage of GBC, and involvement of surrounding lymph nodes in the porta hepatis and peripancreatic area [71, 72]. Additionally, EUS allows for ultrasound directed biopsy of suspicious lymph nodes. The collective functions of EUS make it one of the most recommended modalities to differentiate benign and malignant portal nodes.

Cross sectional imaging of the abdomen utilizing computed tomography (CT) and magnetic resonance imaging (MRI) can provide valuable information about the extent of the disease and its proximity to the surrounding structures. CT scans can detect the presence of polypoid lesions bulging into the gallbladder lumen as well as characterize the pattern of wall thickening. The presence of asymmetrical wall thickening on CT with 3D reconstruction is a strong predictor of malignancy [73, 74]. Other findings suspicious of malignancy include a thick enhancing inner layer of the gallbladder ≥2.6 mm, with a thin outer layer ≤3.4 mm, strong enhancement of the inner wall and irregular wall contour [75]. CT scan images also allow for the detection of lymph node metastasis, vascular invasion, or local involvement of the liver with an overall accuracy of 71–83.9 % for GBC staging [76, 77].

MRI is an essential part of the diagnostic work-up for GBC cases, and a useful tool for staging. MRI is able to examine gallbladder wall thickening, depict soft tissue invasion,

and detect some benign entities, such as adenomas and adenomyomatosis. Studies suggest that MRI in combination with MRA (magnetic resonance angiography) or MRCP (magnetic resonance cholangiopancreatography) is valuable in preoperative evaluation of GBC. Combined MRI and MRCP depict the depth of hepatic invasion, lymph node metastasis, and vascular or biliary tract invasion, allowing for accurate assessment of disease resectability [78, 79].

Positron emission tomography (PET) scan with 18F-flurodeoxyglucose (FDG) is commonly used in cases of suspected malignancy. FDG-PET is useful in differentiating benign from malignant lesions, for staging purposes, and/or for the detection of disease recurrence [80, 81]. The combined FDG-PET is credited with sensitivity of 75–80 % and specificity of 82–100 % for GBC [82, 83]. However, PET scans can show a false positive result when evaluating benign inflammatory conditions [83, 84].

Laboratory Investigations

Various laboratory abnormalities and tumor markers are seen in GBC. Alkaline phosphatase (ALP) and bilirubin levels are typically elevated in cases of bile duct obstruction. Tumor markers, carcinoembryonic antigen (CEA) and carbonic anhydrase (CA19-9) are commonly elevated in GBC, although not diagnostic. CA19-9 at 20.0 units/ml or higher provides a specificity of 79.2 % and a sensitivity of 79.4 % for GBC, while a CEA level of ≥4.0 ng/ml carries a specificity of 92.7 % and a sensitivity of 50 % [85]. These markers play a valuable role in patient follow-up and assessment of response to therapy [86].

Differential Diagnosis

Gallbladder masses include a large spectrum of pathologies beside gallbladder cancers. Other mass-causing lesions include gallbladder adenomyomatosis, found in approximately 1–8 %

of cholecystectomy specimens [87]. Less frequent lesions include tumefactive sludge, and xanthogranulomatous cholecystitis. Metastases, most commonly from melanoma, followed by hepatocellular carcinoma and renal cell carcinoma, are also a part of the differential diagnoses. In the case of diagnostic dilemma, surgical intervention with laparoscopic cholecystectomy and pathological examination is recommended.

Staging Systems

Different staging systems have been proposed for GBC staging based on pathologic factors. One of the most commonly used staging systems is the one developed by the American Joint Committee on Cancer (AJCC); (Table 15.1). The AJCC staging utilizes TNM (tumor, lymph node, metastases) staging for gallbladder cancer and was adopted in 2002. Other commonly used staging systems include the Japanese Biliary Surgical Society system [88], the Nevin system [89], and the modified Nevin system [90] (Table 15.2).

A study performed by Fong et al. examined the AJCC 6th edition accuracy in 10,705 GBC cases diagnosed between 1989 and 1996 from the National Cancer Database (NCDB). The study reported that utilizing the 6th edition staging system provided no discrimination between Stage III and Stage IV patients following 3-year and 5-year survival analyses [91]. The authors proposed a modified staging system, where stage III disease should be divided into stage IIIA encompassing T3N0M0 patients and Stage IIIB consisting of T1-T3N1M0 patients. This suggestion was based on the understanding that lymph node metastases represent different cancer biology. Patients with Stage IVA and stage IVB were also regrouped, where stage IVA contained T4N0M0 patients while stage IVB contained those with nodal metastasis. Recent changes introduced to the AJCC 7th edition in 2010 sought to address the previous edition shortcomings, and provide a better correlation with resectability and patient outcomes (Table 15.3).

Table 15.1 American Joint Committee on cancer staging for gallbladder cancers, 7th edition

	TNM stage		
Stage	T-stage	N-stage	M-stage
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1-3	N1	M0
Stage IVA	T4	N0-1	M0
Stage IVB	Any T	N2	M0
	Any T	Any N	M1

Primary tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1a	Tumor invades lamina propria
T1b	Tumor invades muscle layer
T2	Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or 1 adjacent organ/structure
T4	Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed

(continued)

Table 15.1 (continued)

Stage	TNM stage		
	T-stage	N-stage	M-stage
N0	No regional lymph node metastasis		
N1	Metastasis to nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein		
N2	Metastasis to periaortic, pericaval, superior mesenteric artery, and/or celiac lymph nodes.		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		

Treatment

Surgical Management

Surgical resection remains the mainstay of GBC management and the only potentially curative therapy. Unfortunately, most patients present with an unresectable disease at the time of diagnosis. Although a laparoscopic approach for early stage GBC resection has been proposed, open surgery remains generally recommended due to the risk of gallbladder perforation and subsequent peritoneal seeding in laparoscopic operations [92–94]. Usually, a staging laparoscopy is performed immediately preceding open surgery to exclude peritoneal carcinomatosis. Benefits of laparoscopy include less associated pain, hospital stay and morbidity. Staging laparoscopy is able to identify 23–48 % of unresectable cases, thus reducing the number of nontherapeutic open operations [95, 96].

Patients with stage 1 disease are generally categorized as T1a and T1b based on the tumor invasion into the muscular layer. T1a patients can achieve cure from a simple cholecystectomy [97, 98]. In most instances, these tumors are discovered postoperatively on histological examination of a cholecystectomy specimen, and require no further intervention. However, patients with a T1b tumor usually present with

a high rate of locoregional recurrence if treated with simple cholecystectomy, and thus are managed with an extended cholecystectomy (gallbladder is removed en bloc with liver gallbladder bed). Extended cholecystectomy is reported to improve survival compared to simple cholecystectomy for patients with T1b tumors, although associated with higher perioperative mortality [99].

Stage II tumors invade the perimuscular connective tissue, and have typically received a radical cholecystectomy with liver resection [100–103]. Regional lymphadenectomy is performed as it provides a survival benefit for stage II disease patients [104]. Current management no longer mandates a formal segmentectomy but rather a negative hepatic resection margin.

Patients with Stage III disease have direct tumor invasion into the liver through the gallbladder serosa or lymph node metastasis. Treatment involves radical resection of the gallbladder en bloc with a portion of liver segments IVb and V, and regional lymphadenectomy [103]. Tumor extension to the adjacent structures (colon, duodenum, or stomach) necessities en bloc resection based on anatomic involvement. Patients with disease extending to the cystic and/or bile duct require common duct resection. Frozen section of the cystic duct stump guides the necessity of common duct removal.

Stage IV disease is often unresectable due to extension to surrounding organs and/or vasculature. Major resections are associated with increased morbidity without noticeable survival benefit [101]. For cases with distal nodal involvement (N2 disease), the curative role of resection becomes futile, and referral to palliative treatment should occur.

Management of Incidentally Discovered GBC

Due to the large number of cancer cases discovered intraoperatively or on the postoperative pathologic report, a high index of suspicion should be maintained. Suspicion should be higher in patients with characteristics such as porcelain gallbladder, large polyps of the gallbladder, long standing gall

Table 15.2 Comparison between different staging systems used in gallbladder cancer

Stage	AJCC; 7th edition	Japanese classification	Modified Nevin classification
I	Carcinoma invading mucosal or muscular layer; T1N0M0	Carcinoma confined to gallbladder beyond the capsule	Carcinoma in situ
II	Transmural invasion, no extension beyond the serosa; T2N0M0	Suspicious liver or bile duct invasion + N1	Mucosal or muscular layer invasion
III	Local invasion of nearby organ; T1-T3, N0-N1, M0	Marked hepatic or bile duct invasion + N2 or N3	Transmural and direct liver invasion
IV	Major vascular invasion or invasion of nearby organs or distant metastasis T4, N0-N1, M0; Any T, N2, M0-M1	Extensive hepatic and bile duct invasion, liver and peritoneal metastasis	Lymph node metastasis
V			Distant metastases

stones and/or recurrent gallbladder infection. If a suspicious lesion was discovered intraoperatively, frozen section examination should guide subsequent management. In cases diagnosed postoperatively requiring further surgical management beyond simple cholecystectomy, or if the surgeon is unfamiliar with complex liver resections, referral to an experienced center should occur [102, 105].

Stenting

A large number of GBC patients tend to present with unresectable disease. In these patients, palliative measures are employed to alleviate pain and other symptoms, such as jaundice, pruritus, gastrointestinal obstruction, and cholangitis. Cases presenting with obstructive symptoms were previously

Table 15.3 Comparison between AJCC 6th and 7th edition

Difference between AJCC 6th edition and AJCC 7th edition		
Sixth edition		Seventh edition
Tis = Carcinoma in situ T1 = Tumor invades lamina propria (T1a) or muscle layer (T1b) T2 = Tumor invades perimuscular connective tissue T3 = Tumor perforates serosa and/or invades the liver or adjacent organs T4 = Tumor invades main portal vein or hepatic artery, or multiple extrahepatic organs	T-stage	Tis = Carcinoma in situ T1 = Tumor invades lamina propria (T1a) or muscle layer (T1b) T2 = Tumor invades perimuscular connective tissue T3 = Tumor perforates serosa and/or invades the liver and/or one adjacent organ T4 = Tumor invades main portal vein or hepatic artery or multiple extrahepatic organs
N0 = No regional nodal metastases N1 = Positive regional nodal metastases	N-stage	N0 = No regional nodal metastases N1 = Metastases to nodes along cystic duct, hepatic artery, common bile duct, and/or portal vein N2 = Metastases to pericaval, periaortic, superior mesenteric artery, and/or celiac artery nodes
M0 = No distant metastases M1 = Distant metastases	M-stage	M0 = No distant metastases M1 = Distant metastases

considered for bypass surgery to provide adequate drainage [106]. However, the development of percutaneous interventions and advances in endoscopic procedures provide valuable alternatives that carry less morbidity [107, 108]. Palliative interventions aim to improve symptoms although a recent study questioned their impact on patients' quality of life [108].

Nonsurgical Management

Chemotherapy may provide potential survival benefit for patients with unresectable disease. Recent studies reported a

potential benefit of gemcitabine, alone or in combination with other regimens, for patients with advanced biliary tract cancers [109–111]. Following the results of the ABC-02 trial from the UK, current practice often focuses on gemcitabine with cisplatin in the treatment of biliary tract disease including gallbladder cancer [112].

Radiation therapy (RT) efficacy in patients with unresectable GBC and CC has been reported. Houry et al. suggested that an intraoperative "boost" of 15Gy of radiation followed by 40–50Gy of external radiation postoperatively might provide a survival benefit [113]. A study examining a cohort of 4180 GBC patients from the SEER database reported that RT provided a survival benefit for patients with stage ≥T2 stage disease with nodal metastases [114]. The 2-year survival rates improved from 17 to 33 % and the median survival from 9 months to 14 months following the delivery of RT. The impact of combination RT and chemotherapy for GBC is unknown [115].

Conclusion

In conclusion, gallbladder cancer is a disease with a poor prognosis. Risk factors are not well understood, and are largely centered on gallstones, porcelain gallbladder, and polyps. Current imaging advances have allowed the identification of patients that would benefit most from surgical intervention. Laparoscopy is usually performed to assess the extent of disease and guide the operative decision. Surgery remains the only curative option and provides promising results in patients with early disease. Stenting through a percutaneous or endoscopic approach may palliate symptoms in advanced stages. While radiotherapy may provide survival benefit for patients with disease stage ≥T2, patients with widespread disease currently benefit most from chemotherapy regimen of gemcitabine and cisplatin.

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