Gallbladder Cancer

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KEYWORDS

• Gallbladder cancer • Radical cholecystectomy • Port site recurrence
• Biliary tract malignancy • Incidental gallbladder cancer

KEY POINTS

- Gallbladder cancer remains a disease with poor overall prognosis.
- Chronic inflammatory conditions of the gallbladder are associated with gallbladder cancer.
- T stage translates into the likelihood of identifying residual disease at reoperation for incidental gallbladder cancer, and residual disease negatively impacts survival.
- In select patients with radical operative intervention, there is an improvement in survival if R0 (margin negative) resection is achieved.
- There is no difference in survival in patients undergoing staged curative resection versus single-stage radical operation.
- Port site involvement of disease is predictive of poor outcome, often correlating with the presence of carcinomatosis.
- Improved systemic therapy is paramount to improving the overall survival in patients with gallbladder cancer.

INTRODUCTION

Gallbladder cancer remains a relatively rare malignancy with a highly variable presentation. Gallbladder cancer is the most common biliary tract malignancy with the worst overall prognosis. With the advent of the laparoscope, in comparison with historical controls, this disease is now more commonly diagnosed incidentally and at an earlier stage.[1–4] However, when symptoms of jaundice and pain are present, the prognosis remains dismal.[5] From a surgical perspective, gallbladder cancer can be suspected preoperatively, identified intraoperatively, or discovered incidentally on final surgical pathology.

INCIDENCE AND EPIDEMIOLOGY

Biliary tract cancers include intrahepatic bile duct cancers, extrahepatic bile duct cancers, and gallbladder cancers. These adenocarcinomas all arise from the biliary

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epithelium, with gallbladder cancer being the most common.[6] There will be an estimated 10,310 new cases of gallbladder and extrahepatic biliary tract cancers diagnosed in 2013. This subset is the sixth most common gastrointestinal malignancy, with gallbladder carcinomas composing most of this group.[6]

Worldwide, there are regional variations in the incidence of gallbladder cancer. Central and Northern European, Indian, and Chilean populations have a higher incidence of gallbladder cancer when compared with the overall US population. The incidence rates of gallbladder cancer in Chile are more than 25 per 100,000 females and 9 per 100,000 males. These rates far exceed those that are found in the United States. The US incidence rates for gallbladder cancer are 0.9 and 0.5 per 100,000 females and males, respectively.[7] Racial discrepancies are also found with gallbladder cancer in the United States. American Indians, Alaskan natives, Asian Pacific/Islanders, blacks, and Hispanics all have a higher incidence when compared with non-Hispanic whites.[8–10]

As with most malignancies, the incidence of gallbladder cancer increases with age. The mean age at diagnosis is 65 years.[11] There is a strong predilection for gallbladder cancer among women, with female-to-male ratios varying from 1.3 to 3.5:1.0.[8,11–13] Sex and ethnicity are further discussed later as they relate to risk factors for this disease.

RISK FACTORS

Most gallbladder cancers are adenocarcinomas arising from the gallbladder mucosa. It is thought that chronic inflammation of the gallbladder mucosa may trigger progression from dysplasia to carcinoma in susceptible patients. Most of the known risk factors associated with gallbladder cancer are related to inflammation.[14]

Gallstones

The development of cholelithiasis is multifactorial in nature. Some of the risk factors for the development of cholelithiasis include age, sex, race, parity, and rapid weight loss.[15] Within the United States, cholesterol stones are the predominant stone type and are formed as a result of cholesterol supersaturation of bile, accelerated cholesterol crystal nucleation, and impaired gallbladder motility.[16] As discussed later, there is a potential genetic association that independently increases the risk of cholelithiasis and, thus, gallbladder cancer.[17,18]

There is clearly an association between benign gallstones and gallbladder cancer.[19–22] Piehler and Crichlow's[23] review of more than 2000 patients with gallbladder cancer found that 73.9% of patients had stones present. Other investigators have found similar results. Most patients (70%–88%) who present with gallbladder cancer have a history or presence of stones, but the incidence of gallbladder cancer among patients with stones is only 0.3% to 3.0%.[4,13,19,24] Diehl[24] showed that there is an increased association with gallbladder cancer as the size of gallstone increases. Although this is a graded phenomenon, stone size greater than 3 cm is thought to confer an up to 10 times increased risk of gallbladder cancer.[24] Roa and colleagues[25] showed that patients with gallbladder cancer will have an increased volume, weight, and density of their gallstones. Gallstone volume is associated with increased relative risk (RR) for developing gallbladder carcinoma, with volumes of 6 mL and 10 mL having RRs of 4.92 and 11.0, respectively.[25]

Gallbladder Polyps

Most polyps are not adenomatous, and most gallbladder cancers do not arise from polyps; however, removal of gallbladders containing polyps greater than 10 mm is recommended for cancer risk reduction.[26,27]

Polypoid lesions of the gallbladder greater than 10 mm, or those showing rapid growth, have classically been associated with gallbladder cancer.[22,28–31] An association between patient age and polypoid lesions containing malignancy has been shown. There is an increased risk for cancer with patients older than 50 years and polyps larger than 10 mm; thus, many surgeons will recommend elective cholecystectomy for this population.[30,32–34] Gallbladder polyps greater than 10 mm in patients older than 60 years and associated with gallstones were shown by Terzi and colleagues[34] to have an increased risk of being malignant in nature. In patients with polyps greater than 10 mm, 88% were found to harbor malignancy and 15% were thought to be benign.[34]

Infection

Bacterial-induced chronic inflammation has also been implicated as a risk factor for gallbladder cancer. Hepatobiliary cancers have been linked to specific bacterial infections, most notably *Salmonella typhi*.[21,22,35,36] Caygill and colleagues[35] demonstrated that chronic typhoid or paratyphoid carriers will have a significantly elevated risk (167 times observed/expected) of gallbladder cancer. Bile acid analysis demonstrated *Salmonella typhi* in 40% of patients with gallbladder cancer compared with 8% of patients with simple cholelithiasis, thus, suggesting that typhoid infection carries a stronger correlation with gallbladder cancer than simple cholelithiasis.[37] Typhoid-endemic areas, such as Chile, have an increased risk of gallbladder cancer.[18] Additionally, previous reports from India have shown an association with chronic typhoid carriage and gallbladder cancer.[38]

Anomalous Junction

Anomalous junction of the pancreaticobiliary ductal system (AJPBDS) has also been implicated as a potential risk factor for gallbladder cancer.[21] This anomaly will typically allow reflux of pancreatic fluid into the common bile duct and bile reflux into the pancreatic duct. The act of regurgitation can lead to inflammation and metaplasia within the gallbladder, thus, presenting a potential mechanism for adenocarcinoma pathogenesis.[39] The bile duct has a lower hydrostatic pressure than that found in the pancreatic duct; therefore, patients with AJPBDS have an increased propensity of flow from the pancreatic duct into the bile duct. Tanaka and colleagues[40] found that 17.8% of patients with AJPBDS developed a coexistent carcinoma, concluding that AJPBDS increases the risk of malignancy, including gallbladder cancer. Kang and colleagues[41] demonstrated that not only is there an increased incidence of gallbladder cancer with AJPBDS but that adenocarcinoma in this population tends to present at a younger age.

Porcelain Gallbladder

Porcelain gallbladder was once thought to significantly increase the risk of gallbladder cancer, as published by Etala[42] in 1962. In that study, there was a 12% to 61% incidence of gallbladder cancer among those patients with a calcified gallbladder. In the past 15 years, this has been refuted with studies showing a much lower incidence (5%–6%) of cancer associated with a calcified gallbladder.[43,44] Towfigh and colleagues[45] looked at 10,741 cholecystectomy patients, 15 of whom had a porcelain gallbladder. Of those 15 patients, none had evidence of gallbladder carcinoma. Stephen and Berger[43] found that the pattern of gallbladder wall calcification can depict its malignant potential. Although they showed an overall incidence of 5% malignancy associated with calcified gallbladder, a pattern of nondiffuse mucosal calcification carried an increased risk of malignancy. There continues to

be a risk associated with calcified gallbladders, but the risk is more likely related to the inflammatory condition resulting in the porcelain gallbladder as opposed to the porcelain gallbladder itself. Porcelain gallbladder is minimally a surrogate for inflammation; given that gallbladder mucosal inflammation is a risk factor for gallbladder cancer, porcelain gallbladder remains an indication for cholecystectomy in appropriate patients.

Genetics

Given the epidemiology with known high-risk populations, a specific genetic link has been sought. Miguel and colleagues[17] showed a specific genetic link between cholesterol-laden bile and specific populations. Even without the typical lithogenic risk factor of obesity, specific ethnic groups with Amerindian maternal lineage in the Chilean population have an increased prevalence of gallstone formation thought to be associated with mtDNA polymorphisms. These factors support the theory of a genetic predisposition found within specific ethnic populations.[17,18] With previous work showing that cholelithiasis carries an increased risk of gallbladder cancer, and now a genetic link with lithogenic bile in specific populations, it may be inferred that there is a genetic risk for the development of gallbladder cancer.

There also seems to be a familial component that carries an increased risk for gallbladder cancer.[46,47] The Swedish Family Cancer Database has shown there is a 5.1-fold increased risk for developing gallbladder carcinoma when a parent had a diagnosis of gallbladder cancer.[47] An Italian case report found an RR of 13.9 for gallbladder cancer among first-degree relatives.[46] A cohort study from the United States found an association among first-degree relatives with an RR of 2.1,[48] although it is unclear whether this is genetic or environmentally based.

Sex

Worldwide, the incidence of gallbladder cancer is generally about double in females versus males. Norway, with an overall low incidence, has a female-to-male ratio of 2.0, 0.4 per 100,000 versus 0.2 per 100,000, respectively. In Chile, with a comparatively high incidence, the female-to-male ratio is 2.7, 25.3 per 100,000 versus 9.3 per 100,000, respectively. In the United States, the ratio across all ethnic groups is 1.8, female to male.[2,7,49] Although female sex is a risk factor for the development of gallbladder cancer, it has generally been thought to be related to the increased incidence of gallstones in women. That said, a recent study published in *Gene* suggests a sex-specific link to a genetic variant in the prostate stem cell antigen gene associated with gallbladder cancer.[50]

Others

Environmental risks have been demonstrated with specific occupations. The Cancer-Environment Registry study from Sweden found that there is an increased risk of gallbladder cancer in patients who work in the petroleum refining, textile, paper mill, and shoemaking industries.[51,52] There was an increased incidence of gallbladder cancer by 3.8 with petroleum refining workers, and a 1.8 increased incidence with paper mill workers compared with control cohorts.[51] Female workers in the textile industry have an increased RR of gallbladder cancer of 3.19.[52] Rubber industry workers are also thought to have a higher incidence of gallbladder cancer.[23]

Additional associated risk factors include cigarette smoking, drugs, chemical exposure, postmenopausal state, autoimmune disorders, and inflammatory bowel

disease.[2,53,54] Most of the nonepidemiologic risk factors seem to be related to the potential for mucosal inflammation and dysplasia.

ANATOMY

The anatomy of the gallbladder is relatively straightforward, with the gallbladder adherent to the undersurface of the liver along liver segments IV and V. Of course, cystic duct and cystic artery anatomy can be aberrant; but typically the cystic duct joins the main bile ducts defining the junction of the common hepatic and common bile ducts, and the cystic artery is generally a branch of the right hepatic artery. The venous drainage of the gallbladder is predominantly via the liver bed.[55]

The wall of the gallbladder, unless diseased, is thinner than that of other hollow viscus organs because there is no submucosa. The wall of the gallbladder is composed of mucosa, a muscular layer, perimuscular connective tissue, and serosa on the peritoneal surface. The T stage of a gallbladder cancer is anatomically related to the depth of invasion through the wall of the gallbladder. T1a tumors demonstrate invasion of the lamina propria; T1b tumors invade the muscular layer; T2 tumors invade perimuscular connective tissue without extension beyond the serosa or into the liver; and T3 perforates the serosa and/or directly penetrates the liver and/or one other adjacent organ (**Figs. 1** and **2**).[56]

PATHOLOGY

The standards for the evaluation of a cholecystectomy specimen vary. Generally, the specimen is inspected grossly by the pathologist or pathology assistant. If there are no obvious findings, or if clinical history is only that of benign disease, 3 slides are submitted for review: one from the fundus, one from the body, and one from the neck.[57] If a tumor is grossly identified or identified microscopically, additional sections are submitted. A European review that looked at incidental gallbladder cancer noted 13 cases identified only after port site or distant metastatic disease was detected in the face of negative initial surgical pathology from the gallbladder

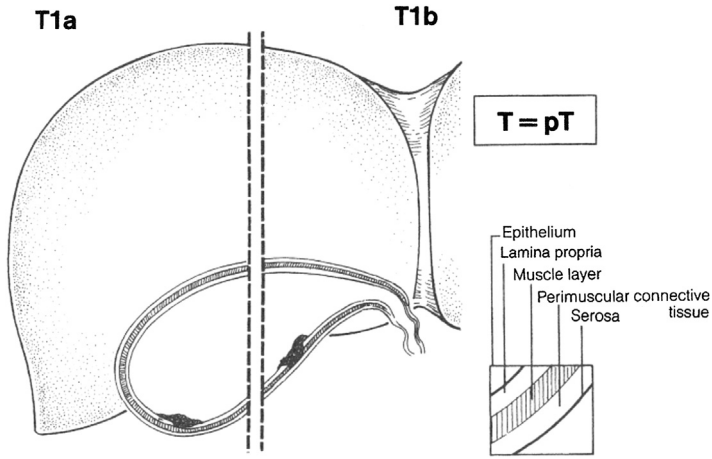

Fig. 1. T1 showing the tumor invading the lamina propria or muscle layer of the gallbladder. (Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.)

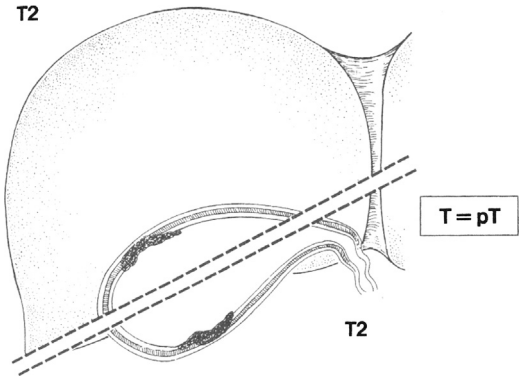

Fig. 2. T2 showing the tumor invading perimuscular connective tissue of the gallbladder with no extension of the tumor beyond serosa or into the liver. (Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.)

specimen.[55,58] If untoward pathologic conditions are suspected by the operating surgeon, a full histologic review of the specimen may be warranted.

STAGING/PROGNOSIS

In 1976, Nevin and colleagues[59] proposed a method that used histologic grading along with staging to determine the prognosis of gallbladder cancer. They stated that stage I and stage II cancers could be cured by simple cholecystectomy with a 5-year survival of 100%. Both stage III and stage IV had a poor prognosis; the 5-year survival rates were 6% and 3%, respectively.[59] In 1978, Piehler and Crichlow[23] reported a 4.1% 5-year survival for all patients and a 16.5% 5-year survival for those who were aggressively surgically resected. Currently, as with most other cancers, the American Joint Committee on Cancer (AJCC) uses the TNM staging system whereby *T* describes the tumor growth within the gallbladder or into adjacent organs, *N* describes lymphatic spread, and *M* indicates any evidence of metastases (**Table 1**).[56]

The seventh edition of the AJCC staging system was released in 2009 and incorporated into practice in 2010. As the stage of gallbladder cancer increases, the prognosis worsens precipitously as depicted in the survival curves (**Fig. 3**,[56] p. 212, **Table 2**). With the most current edition of the TNM staging system, nodal status seems to be the most suggestive of overall prognosis.[56,60] Earlier studies indicated that tumor status was inversely correlated with prognosis.[61,62] Oh and colleagues[60] found that as nodal status increased, regardless of T stage, there was a decrease in 3-year survival rates. Based on a single-center review of patients with gallbladder cancer, the median survival for stages I to III was 12 months, with median survival for stage IV patients being only 5.8 months.[63,64]

As more patients undergo laparoscopic cholecystectomy, the incidence of incidental gallbladder cancer will continue to increase. Proper staging workup is necessary in these patients to help guide treatment recommendations.

PREOPERATIVE IMAGING

Early gallbladder cancer is often associated with sonographic findings mistakable for cholecystitis; however, when more ominous features of malignancy exist, additional

Table 1
American Joint Committee on cancer 7th edition TNM staging for gallbladder cancer

Primary Tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades lamina propria or muscular layer
T1a	Tumor invades lamina propria
T1b	Tumor invades muscular 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 one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4	Tumor invades main portal vein or hepatic artery or invades at least 2 extrahepatic organs or structures
Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases to nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein
N2	Metastases to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes
Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis

Anatomic Stage/Prognostic Groups

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

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imaging is warranted. Specifically, evidence of a lesion, as opposed to simple wall thickening, especially if associated with invasion, vascularity, sessile shape, or adenopathy, should increase the index of suspicion.[26] High-resolution computed tomography (CT) or magnetic resonance imaging may be helpful in determining resectability and ruling out distant disease. Additionally, [18]F-fluorodeoxyglucose (FDG) positron emission tomography (PET) CT may be appropriate for preoperative evaluation. Gallbladder cancer is thought to be highly FDG avid, with PET changing management in almost a quarter of patients in some series.[2,65,66] That said, negative PET imaging does not preclude reresection of incidentally found cancers,

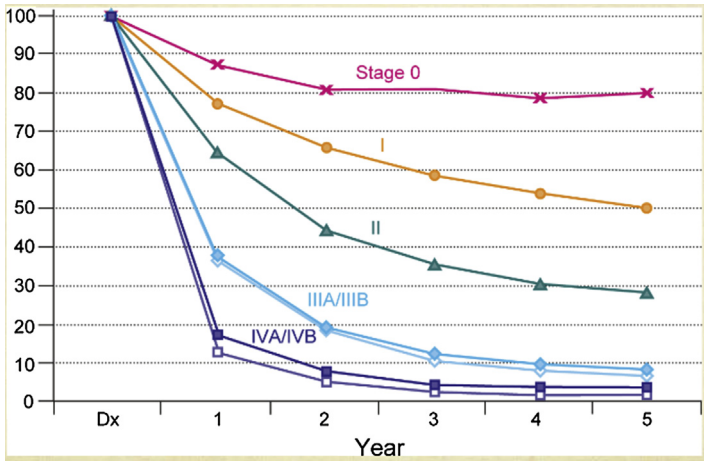

Fig. 3. Observed survival rates for 10,705 gallbladder cancers. Dx, diagnosis. Data from the National Cancer Data Base (Commission on Cancer of the American College of Surgeons and the American Cancer Society) diagnosed in years 1989 to 1996. (Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.)

because clearly small-volume disease or non–FDG-avid disease can be missed on PET.

Although asymptomatic gallbladder cancer discovered on imaging done for other reasons is truly incidental, the diagnosis is known, or at least suspected, by the surgeon preoperatively, thereby allowing additional preoperative evaluation. Whether initial imaging is done for gallbladder-related symptoms or for completely unrelated reasons, an abnormal appearance to the gallbladder may trigger more complex imagining to better define the extent of the disease. Biopsy of distant disease may be warranted for diagnostic purposes, generally to help guide palliative treatment. Biopsy of suspicious but presumably resectable disease is generally unnecessary.

INCIDENTALLY IDENTIFIED GALLBLADDER CANCER

Gallbladder cancer that is unsuspected preoperatively and subsequently discovered either at the time of cholecystectomy or on receipt of surgical pathology is referred to as *incidentally discovered* or *incidental gallbladder cancer*. With the advent of

Table 2
5-year survival rates as depicted in Fig. 3

Stage	5-y Survival Rate (%)
0	80
I	50
II	28
IIIA	8
IIIB	7
IVA	4
IVB	2

laparoscopy and the dramatic increase in the number of cholecystectomies performed, there has been an increase in the number of incidentally discovered gallbladder carcinomas.[1–3,55]

Most cholecystectomies performed in the United States are done laparoscopically. Gallbladder cancer is diagnosed during laparoscopic cholecystectomy or histologically on review of surgical pathology 0.2% to 2.0% of the time.[3,55,67–69] Most patients with gallbladder cancer also have gallstones, making a preoperative diagnosis of stone disease typical. Although the prognosis in this group is highly variable and based on overall staging, patients with incidentally discovered disease have improved survival versus those presenting nonincidentally, despite most patients having residual disease at reoperation.[2,3] Worse prognosis in the non-incidental group likely reflects an increased disease burden in those presenting with a more obvious carcinoma.

OPERATIVE MANAGEMENT

Up to half of all gallbladder cancers are diagnosed pathologically after cholecystectomy for presumed benign disease.[56] It is well recognized that T1a tumors require no further management beyond simple cholecystectomy, assuming negative resection margins.[63] The prognosis for Tis and T1a tumors is good, with 85% to 100% cured after simple cholecystectomy.[70]

In most patients presenting with symptoms from gallbladder cancer, the disease is advanced. The most common presenting symptoms are right upper quadrant pain and jaundice, with jaundice being an independent indicator of poor prognosis.[5,71] More than two-thirds of patients presenting to a tertiary cancer center without prior operation were found, either by imaging or at time of laparotomy, to have unresectable disease.[71]

Clearly, whether disease is incidental or known preoperatively, complete resection of all known disease is the objective of any oncologic procedure. Unfortunately, even with aggressive resectional therapy, R0 resection rates remain suboptimal. Shih and colleagues[1] reported R0 resection rates of 85% in patients with reexplored, incidentally discovered gallbladder cancer and only 25% in patients with primarily explored, nonincidentally discovered gallbladder cancer. Patients who are reexplored in the setting of incidentally discovered gallbladder cancer are a highly selected group, generally with lower tumor burden, likely explaining the improved R0 resection rates. This correlates with improved survival rates in those with incidentally discovered disease.[3]

There has been no difference in survival in patients undergoing staged curative resection (simple cholecystectomy followed by radical reresection) versus single-stage operation for gallbladder cancer. This fact would imply that for surgeons making intraoperative diagnoses of gallbladder cancer, closure and referral to a tertiary center does not adversely impact patient outcomes. This practice is the standard recommendation if the primary surgeon is not comfortable with the management of more complex hepatobiliary disease.[1,71]

Primary Operation (Known or Suspected Malignancy)

Patients presenting with incidentally discovered disease have a better median survival versus those presenting with known disease. Intuitively, patients presenting with symptoms or findings that suggest malignancy, either on history, examination, or imaging, are likely to have more advanced disease at presentation. Regardless, the goal of operative intervention is the same as for those with incidentally discovered disease: achieve an R0 resection. Thorough staging workup is appropriate to rule out distant metastatic disease or locally unresectable disease before proceeding with operative

intervention. Diagnostic laparoscopy is also appropriate in this group, given the significant potential for peritoneal disease.[72] Assuming patients are reasonable operative candidates and that there is no evidence of distant disease or unresectability, proceeding with cholecystectomy, en block liver resection, lymphadenectomy, and bile duct resection, as necessary, is appropriate.[63]

Secondary Operation (After Incidental Discovery of Malignancy)

Repeat operative intervention is often indicated for incidentally discovered gallbladder carcinoma. In patients with margin negative T1a disease (invasion of lamina propria), locally unresectable disease, or distant metastases, there is no role for additional operative intervention.[63]

The National Comprehensive Cancer Network's (NCCN) guidelines recommend reoperation for T1b (invasion into muscular layer), T2 (invasion into perimuscular connective tissue), and T3 (perforates the serosa and/or directly penetrates the liver and/or one other adjacent organ) tumors (see **Figs. 1** and **2**).[56,63] There has been some controversy over the role of aggressive operative intervention in T1b disease; however, a Surveillance, Epidemiology, and End Results (SEER) registry review by Hari and colleagues[73] published in 2012 showed differential survival in patients with T1a versus T1b tumors treated with cholecystectomy alone, further supporting the NCCN's guidelines.

The NCCN's guideline surrounding T2 tumors is based on several reports showing improved survival in patients with T2 tumors undergoing radical cholecystectomy versus cholecystectomy alone.[74,75] A SEER review published in 2007 found that less than 10% of patients with T2 gallbladder cancer were treated based on these recommendations. There are, of course, intrinsic concerns with a retrospective database review; however, these results are concerning and may warrant further investigation.[74]

Residual Disease

In 2007, Pawlik and colleagues[3] published a multicenter review evaluating the likelihood of finding residual disease in patients undergoing reresection for incidental gallbladder cancer. There were 225 patients from 6 international centers included; 148 (65.8%) had incidental gallbladder cancer and 77 (34.2%) had nonincidental disease. The overall median survival of the cohort was 18 months. Of the 148 with incidental disease, 115 had staged operations and 33 had a definitive operation or were determined to be unresectable at the initial intervention. At the time of reoperation, 70 of 115 (60.8%) patients had residual or metastatic disease. Even in patients deemed appropriate for reresection, more than 40% had residual disease after initial cholecystectomy. The T stage correlated with the risk of finding residual disease. Patients with T1, T2, and T3 disease had a 37.5%, 56.7%, and 77.3% chance of having additional disease, respectively. Patients with no residual disease at reoperation had a 5-year survival of 84.8% versus 36.9% ($P = .01$) for those with residual disease.[3]

In a French database review of patients with incidental gallbladder cancer, those patients undergoing reexcision had a better overall survival at 1 year: 76% in the reresection group (n = 148) and 52% (n = 70) in the no reresection group.[76] Of those undergoing reresection, 56% were found to have residual disease. In this retrospective review, reasons for not undergoing reresection included age and T stage; specifically, no T1a patients underwent reresection.[76] One of the limitations with this and other similar studies is the difficulty in knowing the true stage of the unresected group. Clearly, there are patients who are thought clinically to be T2 who

actually have peritoneal disease, possibly skewing the data in favor of the reresection group.[76]

Management of the Liver Bed

Gallbladder cancer has the potential to spread via direct extension into the liver, along the ducts, or into adjacent organs. Metastatic disease can also be disseminated via the peritoneum, the lymphatic system, and/or hematogenously. The gallbladder lies anatomically along the caudal aspect of the liver at the junction of the left and right lobes, allowing for direct invasion into the liver at this site.

Some have advocated radical liver resection for gallbladder cancer. Dixon and colleagues[77] compared 2 time periods, with the more contemporary time period representing more radical liver resection based on a change in disease management strategy. There was improved overall survival in the contemporary group undergoing more radical liver resection versus the earlier group. Survival rates in both periods were similar in the R0 and R1 resection groups; however, more R0 resections were achieved in the period of radical resection. They concluded that R0 resection improves overall survival in patients undergoing curative resection for gallbladder cancer and that radical resection improves the likelihood of obtaining a negative resection margin.[77] In that series, radical resection (2 to 6 liver segments) was associated with a complication rate of 49% (major complications requiring intervention in 29%) and a mortality rate of 2%.[77]

Pawlik and colleagues[3] reviewed 97 patients undergoing hepatic resection (wedge resection vs formal segmentectomy vs hemihepatectomy) at the time of reoperation for incidental gallbladder cancer and found that the extent of hepatic resection was not associated with a survival benefit. The likelihood of finding additional disease in the liver correlated with the T stage, with 0%, 10.4%, and 36.4% having hepatic disease at the time of reresection for incidentally identified T1, T2, and T3 gallbladder cancer, respectively.[3]

Other studies have also shown that the extent of liver resection and bile duct resection did not impact survival and that more extensive resections may instead only increase morbidity.[1,70,76,78] In most cases, extended hepatectomy is unnecessary. Although there are clearly large variations in extent of liver resection performed for curative intent, the inability to achieve an R0 resection may be an indicator of aggressive biology and, as such, a marker of poor prognosis.

Management of the Cystic Duct Stump and Extrahepatic Bile Ducts

Some surgeons perform extrahepatic bile duct resection as part of a standard radical resection for gallbladder cancer; others advocate this approach to facilitate nodal dissection; and some selectively perform bile duct resection only for a positive cystic duct margin.

As with residual liver disease, cystic duct margin positivity correlates with the likelihood of finding residual ductal disease at reresection. Residual ductal disease was identified in only 4.3% (1 of 23) of patients with pathologically negative cystic duct margins but was found in 42.1% (8 of 19) of those with positive cystic duct margins. In all reresected patients with incidental gallbladder cancer, residual disease was identified in the bile ducts in about 20%.[3] Although bile duct resection was not found to improve lymph node yield for lymphadenectomy, R0 resection rates are thought to be improved in patients undergoing common duct resection in the setting of an initially positive cystic duct margin.[3] Multiple studies have failed to show a survival benefit with extended biliary resection, and the NCCN's guidelines do not

routinely advocate bile duct resection in the setting of a negative cystic duct margin.[1,3,63,76]

Role of Lymphadenectomy

The seventh edition of the AJCC staging manual defines N1 disease as nodal involvement of the cystic duct, common bile duct, portal vein, and/or hepatic artery nodes.[56] N2 disease involves periaortic, pericaval, celiac, and/or superior mesenteric artery lymph nodes (see **Table 1**). N2 disease is stage IVB disease, and there is no role for aggressive resection.

T stage is thought to correlate with the likelihood of regional nodal metastases at reresection in patients with incidentally discovered gall bladder cancer: T1 (12.5%), T2 (31.2%), and T3 (45.5%).[3] Although there is no proven survival benefit to lymphadenectomy, nodal status is an important prognostic feature; therefore, routine lymphadenectomy is recommended in T1b and higher resectable gallbladder cancers with clinical N0 or N1 disease.[63,79]

In a retrospective review of patients undergoing reoperation for incidentally discovered gallbladder cancer, Pawlik and colleagues[3] found pathologic evidence of nodal metastases in 16 of 24 patients, with at least one cystic duct node evaluated with the initial cholecystectomy specimen. In those undergoing subsequent lymphadenectomy, a median of 3 nodes was resected, regardless of whether the lymphadenectomy was done in conjunction with a common bile duct resection.[3] This finding suggests that, despite some proponents of common duct resection for facilitation of lymphadenectomy, the yield of the nodal harvest may not be improved despite a more radical approach and associated increased morbidity.[3,70,78]

Diagnostic Laparoscopy

Gallbladder cancer has a high rate of peritoneal disease, with carcinomatosis identified in 30% to 75% of patients.[2] In 2002, Weber and colleagues[72] published a prospective series of 100 patients evaluating the use of diagnostic laparoscopy for biliary tract malignancy. Of the 100 eligible patients, 44 had a primary gallbladder cancer, with 21 of 44 having disease identified at time of laparoscopy that precluded laparotomy. Of those with disease identified at the time of laparoscopy, 15 had peritoneal metastases and 6 had previously undiscovered liver metastases. The other 23 patients went on to laparotomy, with 15 of those subsequently determined to be unresectable because of peritoneal disease in one patient, liver disease in 2 patients, extensive nodal disease in 3 patients, and locally advanced unresectable disease in 9 patients. Although laparoscopy did not prevent nontherapeutic laparotomy in all cases, 48% of patients were spared more extensive operative exploration with presumably faster recovery and shorter time to the onset of palliative treatments.[72] In a disease with a median survival of only about 5 months in the setting of unresectable disease, extended surgical recovery is potentially unwarranted. That said, without laparotomy, it is difficult to determine local resectability.

In another series evaluating cases of suspected gallbladder cancer, 5 of 54 were unresectable by preoperative imaging, 1 refused further surgery, and 48 of 54 underwent surgical exploration.[1] Of the 48 explored patients, 15 (31%) were deemed unresectable at laparotomy, 5 (10%) were deemed unresectable at laparoscopy, and 28 (58%) went on to have resectional therapy.[1]

The yield of staging laparoscopy decreases in patients with incidentally discovered gallbladder cancer likely because of decreased disease burden or identification of metastatic disease at the initial operation making them ineligible to present for subsequent laparoscopy. As few as 20% of patients will be found to have advanced disease

in the subgroup of incidentally discovered gallbladder cancer,[72] possibly limiting the utility of laparoscopy in those patients having undergone a recent laparoscopic cholecystectomy.

Port Site Management

In the modern era, most gallbladder cancers are identified incidentally after laparoscopic cholecystectomy done for presumed stone-related symptoms. Because gallbladder cancer has a high propensity for peritoneal seeding and carcinomatosis, port site recurrence is a relatively common phenomenon after laparoscopic cholecystectomy in the setting of incidentally discovered gallbladder cancer. In some series, subsequent port site tumoral involvement can be as much as 10%, with a range from 1% to 40%.[1,3,76,80]

Maker and colleagues[80] reviewed their data on port site involvement in 69 patients having T1b, T2, or T3 disease who had port sites resected at the time of radical resection. They reported that 19% of patients (13 of 69) with port site resection had pathologic involvement; however, this was only seen in patients with T2 and T3 disease. Although port site resection was not associated with improved survival, patients with port site involvement had a worse prognosis, as this seemed to indicate more advanced disease and often carcinomatosis. Of patients with port site involvement, 77% also had peritoneal metastasis.[80]

Port sites other than the original extraction port can be involved, with tumor highlighting the potential for diffuse peritoneal dissemination in addition to direct tumoral seeding. Although extraction site, mode of gallbladder extraction, and occurrence of perforation may impact the decision to resect trocar sites at the time of subsequent operation, resection is unlikely to improve survival; port site involvement remains a marker of poor prognosis.

ADJUVANT THERAPY/PALLIATIVE THERAPY

Clearly, complete surgical resection offers the best chance of cure for patients with gallbladder cancer. There are currently no recommendations for neoadjuvant treatment in patients with locally advanced gallbladder malignancy. Adjuvant treatment, however, continues to be recommended regularly.[2,63,81,82] Per the NCCN's guidelines, there are no definite standard regimens supported by randomized controlled trials and no proven benefit to any adjuvant treatment. Multiple adjuvant therapy regimens are used, and observation continues to be an acceptable option after resection.[63]

The Mayo Clinic reviewed their outcomes in patients with R0 resectional therapy, comparing those with subsequent adjuvant therapy with those without.[83] There were 73 patients included in this retrospective review spanning 20 years, with 43 (59%) T1-2N0M0 and 30 (41%) T3N0M0 or T1-3N1M0. Adjuvant therapy usually consisted of combined chemotherapy and radiation. The overall survival was similar in the group receiving adjuvant therapy and the group that underwent surgery alone, although patients with more advanced disease tended to have adjuvant therapy.[83]

Although evidence to definitively support adjuvant treatment in gallbladder cancer is lacking, Sharma and colleagues[81] randomly assigned 81 unresectable patients to one of 3 arms: best supportive care, fluorouracil and folinic acid, and modified gemcitabine and oxaliplatin. The median overall survival was 4.5, 4.6, and 9.5 months, respectively.[81]

Given the overall poor prognosis of this disease, palliative strategies continue to evolve. Palliative percutaneous or endoscopic biliary drainage may improve symptoms related to malignant biliary obstruction. Combinations of chemotherapy and

radiation may improve survival and quality of life, with gemcitabine used in most adjuvant and palliative regimens for gallbladder cancer.[82] Clearly improved systemic therapy is paramount to improving overall survival in patients with gallbladder cancer.

SUMMARY

A historical series in the natural history of gallbladder cancer published in *Cancer* in 1978 reported an overall median survival of 5.2 months.[4] Although this is similar to the 5-year survival seen in current stage III and IV patients, more gallbladder cancers are presently being diagnosed incidentally, at earlier stages, and with better prognoses. Gallbladder cancer remains a challenging disease in terms of prognosis, preoperative diagnosis, surgical management, and systemic treatment.

Surgical management, with R0 resection as the objective, offers the best prognosis with the only hope of cure. With T1a tumors, this usually occurs at the time of cholecystectomy accounting for the significantly better survival in this group despite the typical recommendation for no additional operation. Many T2 patients are not treated based on current recommendations, leaving room for improvement in the surgical treatment of gallbladder cancer.[74,84]

Studies suggest that if R0 resection is achieved with reoperation for incidental gallbladder cancer, survival is improved. No residual disease at the time of reoperation is also a marker for improved prognosis[3]; in the setting of R0 resection, more radical liver and bile duct resections do not seem, in some series, to improve survival.[1,70,76,78] The stage of disease, as a surrogate for tumor biology, is the most important predictor of complete resectability and, therefore, outcome in gallbladder carcinoma.[3,70,78] Improved systemic therapy will be critical in improving long-term outcomes for these patients.

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