Gallbladder cancer: Epidemiology, risk factors, clinical features, and diagnosis

AUTHOR: Bhoomi Mehrotra, MD
SECTION EDITORS: Kenneth K Tanabe, MD, Christopher G Willett, MD
DEPUTY EDITOR: Sonali M Shah, MD

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INTRODUCTION

Gallbladder cancer (GBC) is an uncommon but highly fatal malignancy; fewer than 5000 new cases are diagnosed each year in the United States. The majority are found incidentally in patients undergoing exploration for cholelithiasis; a tumor will be found in 1 to 2 percent of such cases [1,2]. The poor prognosis associated with GBC is thought to be related to advanced stage at diagnosis, which is due both to the anatomic position of the gallbladder, and the vagueness and nonspecificity of symptoms.

Here we will discuss the epidemiology, risk factors, clinical features, and diagnostic evaluation of GBC. Treatment of localized, potentially resectable GBC and treatment for advanced disease are covered separately, as is cholangiocarcinoma. (See "Prognosis and adjuvant treatment for localized, resected gallbladder cancer" and "Treatment of advanced, unresectable gallbladder cancer" and "Epidemiology, pathogenesis, and classification of cholangiocarcinoma" and "Clinical manifestations and diagnosis of cholangiocarcinoma".)

EPIDEMIOLOGY

Worldwide, there is prominent geographic variability in GBC incidence that correlates with the prevalence of cholelithiasis. High rates of GBC are seen in South American countries, particularly Chile, Bolivia, and Ecuador, as well as some areas of northern India, Pakistan, Japan, Korea, and

Poland [3-5]. In Chile, mortality rates from GBC are the highest in the world. These populations all share a high prevalence of gallstones and/or salmonella infection, both recognized risk factors for GBC [6-8]. Both genetic factors and socioeconomic issues that delay or prevent access to cholecystectomy for gallstones are thought to be contributory [9,10]. (See 'Risk factors' below and 'Histology and molecular pathogenesis' below.)

North America is considered a low-incidence area. Estimates from the Surveillance, Epidemiology, and End Results (SEER) database reveal an incidence of 1 to 2 cases per 100,000 population in the United States; incidence is higher in females than in males (1.7 versus 1.0 cases per 100,000 per year) [11]. In contrast to the general population, GBC is the most common gastrointestinal malignancy in both Southwestern Native Americans and in Mexican Americans [12].

Although the available data support a decreased overall incidence of GBC in the United States over the last 30 years, the incidence may be increasing in younger individuals [13,14]. Globally, the burden of gallbladder and other biliary tract cancers has risen over the last 30 years [15].

In addition to geography, there are also age, race, and gender-related differences in the incidence of GBC. Incidence steadily increases with age, women are affected two to six times more often than men [11,16,17], and GBC is more common in White compared with Black people [18].

RISK FACTORS

Several risk factors have been identified for GBC, many of which share a common characteristic of chronic gallbladder inflammation [3,12,19-21].

Gallstone disease — Gallstones are present in 70 to 90 percent of patients with GBC [20,22], and a history of gallstones appears to be one of the strongest risk factors for the development of GBC [4,20,21,23-25]. As an example, in a case-control study from Shanghai that included 368 patients with GBC and 959 healthy controls, individuals with symptomatic gallbladder disease (gallstones or self-reported cholecystitis) were 34-fold more likely to develop GBC [20]. Seventy to 90 percent of gallbladder cases have a history of cholelithiasis [26].

Despite the increased risk of GBC in patients with gallstones, the overall incidence of GBC in patients with cholelithiasis is only 0.5 to 3 percent [27,28]. The risk is higher with larger gallstones (in one study, patients with stones larger than 3 cm had a 10-fold higher risk of GBC compared with those with stones <1 cm [29]) and longer duration of cholelithiasis (particularly over the age of 40 years [30]). (See "Approach to the management of gallstones".)

Porcelain gallbladder — Porcelain gallbladder is an uncommon manifestation of chronic cholecystitis that is characterized by intramural calcification of the gallbladder wall. It is associated with cholelithiasis in more than 95 percent of cases. As with other gallstone-related conditions, these patients are at increased risk of GBC. The reported incidence of GBC in patients with a porcelain gallbladder ranges from 0 to 60 percent, with more recent studies suggesting a rate of approximately 2 to 3 percent. The increased risk may be confined to patients with selective mucosal calcification or incomplete mural calcification. (See "Porcelain gallbladder", section on 'Epidemiology'.)

Gallbladder polyps — Gallbladder polyps are outgrowths of the gallbladder mucosal wall that are usually found incidentally on ultrasonography or after cholecystectomy. They are classified as benign or malignant, and benign lesions are further classified as nonneoplastic (eg, cholesterol and inflammatory polyps, adenomyomas) or neoplastic (eg, adenomas, leiomyomas) (table 1).

The most common benign neoplastic lesion is adenoma, a glandular tumor composed of cells resembling biliary tract epithelium. It is unclear whether adenomatous polyps represent a premalignant lesion and, if so, with which frequency they progress to carcinoma [31]. Unlike GBC, gallbladder polyps tend not to occur in patients with cholelithiasis, chronic inflammation is generally absent, and cancer-related molecular changes that are seen in GBCs have not been identified in adenomas [31]. Nevertheless, larger polyps are more likely to contain foci of invasive cancer, and some (but not all [32]) studies suggest a correlation between the presence of gallbladder polyps and the risk of GBC [33]. (See "Gallbladder polyps".)

Primary sclerosing cholangitis — A higher risk of gallbladder mass lesions is reported in the chronic inflammatory state associated with primary sclerosing cholangitis [34-36]. In a study of 286 patients, 6 percent of cases were found to have gallbladder masses, of which 56 percent were GBCs [34]. Therefore, an annual screening ultrasound of the gallbladder is recommended in these patients. (See "Primary sclerosing cholangitis in adults: Management", section on 'Gallbladder carcinoma and cholangiocarcinoma'.)

Chronic infection

Salmonella — In endemic settings, approximately 1 to 4 percent of acutely infected individuals become chronic asymptomatic carriers of *Salmonella typhi*. Several reports and a meta-analysis of 17 case-control and cohort studies suggest an association between chronic *S. typhi* carriage and elevated risk of GBC [37-40]. Because chronic carriage occurs more often in individuals with cholelithiasis, gallstones are thought to represent a potential nidus for ongoing infection. (See "Pathogenesis of enteric (typhoid and paratyphoid) fever", section on 'Chronic carriage'.)

Helicobacter — *Helicobacter* colonization of the biliary epithelium (particularly *Helicobacter bilis*) has been implicated in the pathogenesis of gallbladder disease, including GBC, based on detection of *Helicobacter*-derived cytotoxins and surface proteins using sensitive molecular and immunohistochemical techniques [41-45]. The strength of this association requires further clarification.

Congenital biliary cysts — Biliary cysts are cystic dilatations that may occur singly or in multiples throughout the bile ducts. They were originally termed choledochal cysts (involving the extrahepatic bile duct), but the clinical classification was revised in 1977 to include intrahepatic cysts. Biliary cysts may be congenital or acquired, and they are associated with a variety of anatomic abnormalities. An anomalous pancreaticobiliary duct junction is present in approximately 70 percent of patients with biliary cysts. Like anomalous pancreaticobiliary duct junction, biliary cysts are especially frequent in Asian populations. (See "Biliary cysts".)

Biliary cysts are associated with an increased risk of cancer, particularly cholangiocarcinoma. The incidence of malignancy varies with age at initial presentation. In a 1983 review of all published series of biliary cysts, the incidence of cancer was 0.7 percent in patients under 10 years of age, 6.8 percent in patients 11 to 20 years of age, and 14.3 percent in patients over 20 years of age [46]. An incidence as high as 50 percent has been reported in older individuals. At least one study suggests that the increased incidence of carcinoma in biliary cysts is confined to patients with an anomalous pancreaticobiliary duct junction [47]. (See "Epidemiology, pathogenesis, and classification of cholangiocarcinoma" and "Biliary cysts", section on 'Cancer risk'.)

Abnormal pancreaticobiliary duct junction — Anomalous pancreaticobiliary duct junction is a rare anatomic variation in which the pancreatic duct drains into the common bile duct, resulting in a long common channel (usually over 2 cm in length) (image 1). This condition may represent failure of the embryological ducts to migrate fully into the duodenum. This condition is most prevalent in Asians populations, mostly Japanese [48-50].

The long common channel may predispose to reflux of pancreatic juice into the biliary tree since the ductal junction lies outside of the sphincter of Oddi. Elevated sphincter of Oddi pressures have been documented in anomalous pancreaticobiliary duct junction and could also promote pancreaticobiliary reflux. The result is increased amylase levels in bile, intraductal activation of proteolytic enzymes, alterations in bile composition, and presumed biliary epithelial damage, inflammation, ductal distension, and cyst formation.

Anomalous pancreaticobiliary duct junction appears to increase the risk of biliary and pancreatic malignancy even in patients without a biliary cyst or ductal dilation [51-54]. GBC is the most

common malignancy seen in patients with an anomalous pancreaticobiliary duct junction and no bile duct cysts. As a result, prophylactic cholecystectomy is recommended in affected patients. (See "Biliary cysts", section on 'Abnormal pancreatobiliary junction'.)

The molecular pathogenesis of GBC arising in patients with an anomalous pancreaticobiliary duct junction appears to be different from that underlying the development of GBC in the setting of gallstone disease. (See 'Histology and molecular pathogenesis' below.)

Medications — Some drugs have also been implicated in biliary carcinogenesis, including methyldopa, oral contraceptives/menopausal hormone therapy, and isoniazid [55-58]. Others have found no convincing evidence for an association between oral contraceptive use and GBC [59,60].

Carcinogen exposure — Evidence is accumulating that carcinogen exposure may also be involved in the etiology of GBC. An increased risk of GBC has been described in workers in the oil, paper, chemical, shoe, textile, and cellulose acetate fiber manufacturing industries [6,61], and in miners exposed to radon [62]. An increased risk has also been noted in cigarette smokers [63,64] and possibly in those with high levels of exposure to aflatoxin, a mycotoxin that commonly contaminates corn, soybeans, and peanuts, and that has been associated with hepatocellular cancer risk [65].

Obesity — Obesity has been consistently associated with an increased risk for GBC [23,64,66-69]. (See "Overweight and obesity in adults: Health consequences", section on 'Cancer'.)

Elevated blood sugar — Several reports suggest a modest association between diabetes and risk for GBC, but the relationship may be in part mediated by obesity and a higher risk of gallstones in this population [63,70,71].

An association between consumption of sweetened beverages (which raises blood glucose concentration) and GBC was suggested in a prospective analysis of 70,832 Swedish adults enrolled in the Swedish Mammography Cohort and the Cohort of Swedish Men, who were free of cancer and diabetes and who completed a food frequency questionnaire at baseline [72]. Incident cases of biliary tract cancer were ascertained through linkage with the Swedish Cancer Register. With a mean follow-up of over 13 years, after adjustment for other risk factors, women and men in the highest category of combined sugar-sweetened and artificially sweetened beverage consumption had a significantly higher risk of GBC (multivariable hazard ratio for two or more 200 mL servings per day of sweetened beverages compared with no consumption was 2.24, 95% CI 1.02-4.89).

HISTOLOGY AND MOLECULAR PATHOGENESIS

- **Histology** – The histologic classification of primary neoplasms arising in the gallbladder is shown in the table (table 2) [73]. The majority (close to 90 percent) are adenocarcinomas, although other histologic types are occasionally found, including adenosquamous or squamous cell carcinoma, small cell neuroendocrine tumors, lymphoma, and sarcoma [16,74,75]. Compared with adenocarcinomas, squamous cell cancers (SCC) tend to be higher grade, diagnosed at a later stage, and have a worse survival, even after adjusting for the completeness of resection (patients with SCC had a significantly higher rate of margin positivity, 36 versus 29 percent) [76].

  Grossly, GBC can appear infiltrative, nodular, papillary, or a combination of these morphologies. Papillary carcinomas, which can sometimes fill the entire gallbladder, have the most favorable prognosis [73]. (See "Extrapulmonary small cell cancer".)

  Adenocarcinomas originate as mucosal lesions invading the gallbladder wall as they grow. The lack of a well-defined muscularis layer permits early vascular, lymphatic, and neural invasion. Tumors frequently extend outside of the gallbladder, invading adjacent organs, particularly the liver, as they grow.

- **Molecular pathogenesis** – Differences in the demographics, clinical presentation, and gender distribution suggest that there are two key pathways to developing GBC in patients with cholelithiasis and an anomalous pancreaticobiliary duct junction. The main mechanism involves cholelithiasis and resultant cholecystitis and seems to be the driving force in most regions of the world where GBC is strongly associated with gallstone disease, female gender bias, and age over 65 [6].

  It is hypothesized that chronic irritation of the gallbladder mucosa over a period of years may predispose to malignant transformation or act as a promoter for carcinogenic exposure or genetic predisposition. In keeping with this hypothesis, bile samples from patients in endemic areas are more mutagenic than those from patients from low-incidence areas [77]. Despite these data, there is no conclusive evidence linking bile composition to GBC.

  A second mechanism involves anomalous pancreaticobiliary duct junction, which is associated with a relatively high proportion of cases of GBC in Japan [78]. Cancers associated with this condition occur at a younger age, show less female gender bias, and have a lower incidence of associated cholelithiasis.

There are also histologic and molecular differences in GBCs associated with anomalous pancreaticobiliary duct junction and in those associated with gallstones, providing further evidence that two distinct pathogenetic pathways are involved [7]. GBCs arising in Japan in the setting of an anomalous pancreaticobiliary duct junction are characterized by *KRAS* mutations and relatively late onset of p53 mutations [79-82]. By contrast, at least in Chilean patients with cholelithiasis and chronic cholecystitis, *KRAS* mutations are rare, while p53 mutations arise early during multistage pathogenesis [83,84].

Most epithelial cancers are preceded by a series of histologic and molecular changes that evolve over a period of several years or decades. The paradigm in which stepwise accumulation of specific molecular abnormalities characterizes the evolution from premalignant change to invasive cancer is best established in colorectal cancer. (See "Molecular genetics of colorectal cancer".)

Similar to other gastrointestinal tract adenocarcinomas, adenocarcinomas involving the gallbladder progress from dysplasia to carcinoma in situ, and then to invasive cancer. The molecular changes that characterize these sequential changes are less well characterized than those in colorectal cancer [6]. In contrast to colorectal cancer, gallbladder adenomas are rarely found in the context of dysplastic changes; a metaplasia-dysplasia/carcinoma in situ/invasive carcinoma sequence seems far more prevalent than an adenoma/carcinoma sequence [85]. Further, incidentally identified gallbladder adenomas uncommonly harbor cancerous changes and seem to represent an entity with only a small clinical risk. (See "Gallbladder polyps", section on 'Adenomas'.)

There are molecular differences between dysplastic lesions and adenomas that may account for underlying biologic differences. Mutations in catenin beta 1 (*CTNNB1*) are frequent in adenomas but rare in dysplastic/carcinoma lesions. As noted above, *KRAS* mutations have been identified in dysplastic and hyperplastic lesions associated with anomalous pancreaticobiliary duct junction; this anatomic variant is associated with a significant risk for carcinoma, and these tumors consistently demonstrate *KRAS* mutations. The reciprocal relationship between *CTNNB1* and *KRAS* mutations among adenomas and dysplasia/carcinomas, the frequent association of dysplasia with invasive carcinoma, and the less common finding of adenoma in cancer specimens all suggest that gallbladder adenomas represent a distinct biologic process with a relatively low malignant potential, while *KRAS*-mutated dysplastic lesions have a high malignant potential.

Dysplastic changes can be found in the mucosa adjacent to over 90 percent of GBCs [86], and they are relatively frequent in routine cholecystectomy specimens. The entire sequence appears to take approximately 15 years. Symptomatic cholecystitis seldom

appears before the age of 40; the median age for detecting dysplasia is 45 years of age, and for carcinoma in situ, it is 55 years old [87]. Squamous metaplasia is a rare premalignant lesion found in association with invasive squamous cell GBC.

By contrast, in both adults and children with an anomalous pancreaticobiliary duct junction, epithelial hyperplasia with a papillary or villous appearance is present in 39 to 61 percent of cases and is thought to represent a premalignant histologic change in the gallbladder mucosa [78,88,89]. Hyperplasia then progresses to dysplasia, similar to the usual form of GBC.

CLINICAL PRESENTATION

GBC may be diagnosed preoperatively, intraoperatively at the time of surgical exploration for abdominal symptoms attributable to another disease process, or postoperatively upon examination of the gallbladder specimen, typically removed for cholecystectomy due to symptomatic cholelithiasis. (See "Surgical management of gallbladder cancer".)

Patients with early invasive GBC are most often asymptomatic, or they have nonspecific symptoms that mimic or are due to cholelithiasis or cholecystitis. Before ultrasonography and CT became widely available, the preoperative diagnosis rate for GBC was only 10 to 15 percent [90]. However, with an appropriate index of suspicion and better imaging techniques, a preoperative diagnosis may be reached in 75 to 88 percent of cases [91]. Early tumors as small as 5 mm can be recognized as polypoid masses projecting into the gallbladder lumen or as a focal thickening of the gallbladder wall [33,92]. Even so, only approximately 50 percent of GBCs are recognized before operation in contemporary series [16,93].

Among symptomatic patients, the most common complaint is pain, followed by anorexia, nausea, or vomiting. The symptoms of advanced GBC often differ from usual biliary colic and are more suggestive of malignant disease (eg, malaise, weight loss). Patients who present with a symptom complex suggestive of acute cholecystitis more often have earlier stage disease and a better long-term outcome than those who present otherwise [29].

Patients with GBC may also present with obstructive jaundice, either from direct invasion of the biliary tree or from metastatic disease to the region of the hepatoduodenal ligament. This diagnosis should be particularly suspected if a compression of the common hepatic duct by an impacted stone in the gallbladder neck is identified (ie, Mirizzi syndrome). Invasion of tumor into the porta hepatis may also result in duodenal obstruction [94]. The presence of duodenal obstruction implies unresectability. (See "Mirizzi syndrome".)

Physical examination may reveal a palpable gallbladder in a jaundiced patient. Courvoisier sign or Courvoisier Law was originally proposed to be a sign of malignancy (pancreatic, gallbladder) rather than cholelithiasis [95]. However, because there are exceptions to this rule (eg, chronic pancreatitis, parasitic biliary obstruction, congenital choledochal cyst, common hepatic duct obstruction proximal to the takeoff of the cystic duct) [95], the diagnostic utility of this historical sign is limited. (See "Choledocholithiasis: Clinical manifestations, diagnosis, and management", section on 'Physical examination'.)

Rarely, patients present with extra-abdominal metastases (lung, pleura), hepatomegaly, a palpable mass, ascites, or paraneoplastic syndromes (eg, ectopic hormone secretion or acanthosis nigricans). (See "Cutaneous manifestations of internal malignancy", section on 'Acanthosis nigricans'.)

DIAGNOSTIC EVALUATION

Patients with symptomatic cholelithiasis — Since many patients are diagnosed intraoperatively at the time of cholecystectomy for cholelithiasis, an important issue is the screening of patients with symptomatic biliary tract disease for the possibility of coexisting GBC. The overall accuracy of ultrasonography (US) for staging the local and distant extent of a suspected GBC is limited. Additional imaging (typically cross-sectional imaging with computed tomography [CT] or magnetic resonance imaging [MRI]/magnetic resonance cholangiopancreatography [MRCP]) is needed for patients who have concerning findings on US (calcification, a mass protruding into the lumen, loss of interface between gallbladder and liver, direct liver infiltration, gallbladder polyps ≥10 mm, or a thickened gallbladder wall that is not explained by cholecystitis).

Ultrasound — The usual initial diagnostic study for presumed-benign gallstone-related disease is US. Many patients with an incidental GBC are found retrospectively to have had suspicious US findings (eg, a solitary or displaced stone, or an intraluminal or invasive mass) that were not recognized preoperatively [96]. Findings that are suggestive but not diagnostic of GBC include mural thickening or calcification, a mass protruding into the lumen, a fixed mass in the gallbladder, loss of the interface between the gallbladder and liver, or direct liver infiltration.

Small polypoid lesions within the gallbladder may represent adenomas, papillomas, cholesterolosis, or carcinomas. Polyps over 1 cm in diameter are more likely to contain an invasive cancer than smaller ones [92,97,98]. In one series, cancer was found in 23 and 0 percent of polyps larger than and smaller than 1 cm, respectively [98]. Thus, cholecystectomy should be strongly considered for patients with gallbladder polyps >1 cm. Although fine needle

aspiration (FNA) biopsy may be useful to distinguish cholesterolosis from GBC, the distinction between adenoma and GBC is less accurate [99]. (See "Gallbladder polyps".)

The overall accuracy of US for staging the local and distant extent of suspected GBC is limited [100]. In one report of 26 patients, accuracy was only 38 percent, and the sensitivity for detection of liver infiltration or nodal metastases was only 50 percent each [100]. For this reason, additional imaging (typically cross-sectional imaging with CT or MRI/MRCP) is needed for patients who have concerning findings on US, including those with gallbladder polyps ≥10 mm or a thickened gallbladder wall that is not explained by cholecystitis. (See 'Suspicious ultrasound findings or incidental gallbladder cancer at cholecystectomy' below.)

Suspicious ultrasound findings or incidental gallbladder cancer at cholecystectomy — Cross-sectional imaging with CT or MRI/MRCP is needed for patients who have concerning findings on US. In this setting, evaluation of potential resectability is the key factor. Cross-sectional imaging is also recommended for patients who are found to have an incidentally diagnosed GBC following simple cholecystectomy. In this setting, appropriate imaging (and detailed histopathologic analysis of the cholecystectomy specimen) is needed to decide whether further resection is necessary. (See "Surgical management of gallbladder cancer", section on 'Gallbladder cancer diagnosed after gallbladder surgery'.)

Management of patients who are identified intraoperatively as having a likely GBC during cholecystectomy of presumed-benign gallbladder disease is discussed elsewhere. (See "Surgical management of gallbladder cancer", section on 'Gallbladder cancer diagnosed during gallbladder surgery'.)

Computed tomography and magnetic resonance imaging — For patients who present with a US-detected gallbladder lesion that may represent GBC and for those who are found to have incidentally diagnosed GBC following simple cholecystectomy, we recommend cross-sectional imaging with CT (abdomen and pelvis) or MRI/MRCP. This recommendation is consistent with consensus-based guidelines from the National Comprehensive Cancer Network (NCCN) [101] and the European Society of Medical Oncology (ESMO) [102]. If a likely GBC is diagnosed during imaging, evaluation of potential resectability is the key factor. For those with incidentally diagnosed GBC following cholecystectomy for cholelithiasis, appropriate imaging and detailed histopathologic analysis of the cholecystectomy specimen are needed to decide whether further resection is necessary. For those with locally advanced GBC, dynamic cross-sectional imaging (CT or MRI) should include arterial phase images to determine the anatomic course of the hepatic arteries relative to the tumor, which is necessary to determine resectability.

On CT, GBC can appear as a polypoid mass protruding into the lumen or completely filling it, a focal or diffuse thickening of the gallbladder wall, or a mass in the gallbladder fossa with the gallbladder itself being indiscernible [103]; liver invasion, suspected nodal involvement, or distant metastases may be shown [104,105]. Features suggesting GBC complicated by cholecystitis rather than simple cholecystitis include a higher frequency of lymph node enlargement, more-extensive wall thickness, focal irregularity in wall thickness, and less distention of the gallbladder [106].

CT is less helpful in distinguishing benign from malignant polyps [107]. By contrast, dynamic MRI and MRCP can help to differentiate benign from malignant gallbladder lesions in equivocal cases and provide information as to disease extent [108-110]. MRI is particularly useful for visualizing invasion into the hepatoduodenal ligament, portal vein encasement, and lymph node involvement.

The finding of advanced T stage (ie, resectable T4 disease (table 3)) is not a contraindication to attempted resection for tumors that are located in the fundus, although such tumors require major liver resection and possibly resection of a part of the transverse colon as well. (See "Surgical management of gallbladder cancer", section on 'Extended cholecystectomy'.)

Endoscopic ultrasound — Endoscopic ultrasound (EUS) is considered to be more accurate for imaging the gallbladder than extracorporeal transabdominal US, although data are conflicting. EUS is useful both in the detection and differential diagnosis of gallbladder polyps and in staging tumor extent [111]. (See "Gallbladder polyps", section on 'Limited role for additional imaging'.)

- In one report of 194 patients with polypoid lesions <20 mm who underwent both US and EUS, 58 had a cholecystectomy, either because of symptoms or suspicion of neoplasia on EUS [112]. Compared with transabdominal US, EUS more often correctly predicted the histologic diagnosis (97 versus 76 percent) (table 4). In a second series, 89 patients with polyps <20 mm underwent both EUS and US [113]. The sensitivity, specificity, and positive and negative predictive values for the diagnosis of GBC were 92, 88, 76, and 97 percent for EUS, compared with 54, 54, 54, and 95 percent for US.

- EUS is a useful modality to assess the depth of tumor invasion into the wall of the gallbladder [114,115] and for defining lymph node involvement in the porta hepatis or peripancreatic regions.

- EUS also can provide a means of obtaining bile for cytologic analysis, which has a sensitivity of 73 percent for the diagnosis of GBC [116]. Furthermore, EUS-guided FNA is an accurate and safe tool in the evaluation of gallbladder masses [117].

Although EUS is superior to US and is a reasonable option to image the gallbladder in those with gallbladder polyps or suspected cancer, we and others generally rely on cross-sectional imaging (CT or MRI) rather than EUS because of the ability to detect invasion into the liver for surgical treatment planning and to detect the presence of regional lymph node and distant metastases.

Cholangiography — Cholangiography, endoscopic retrograde cholangiopancreatography (ERCP), and percutaneous transhepatic cholangiopancreatography are of little use for patients suspected of having GBC since the gallbladder is not observed in most cases. These procedures may be helpful in the presence of coexisting jaundice and in planning the surgical procedure, as they may indicate tumor growth in intrahepatic biliary ducts or in the common bile duct. In cases with jaundice, ERCP may be necessary for definition of the extent of biliary involvement, as well as for stent placement.

Completing the staging evaluation

Chest computed tomography — Given that distant metastases can affect the lungs and pleura, consensus-based guidelines from NCCN [101] and ESMO [102] recommend cross-sectional imaging of the chest in patients who appear otherwise to be potential candidates for resection. (See 'Stage distribution at presentation' below.)

Positron emission tomography and integrated positron emission tomography/computed tomography — Although some institutions perform a positron emission tomography (PET) scan in patients who appear otherwise to have potentially resectable disease, most do not, and guidelines from NCCN do not recommend PET or integrated PET/CT for patients with a mass on imaging or an incidental finding of GBC, either at surgery or pathologic review. (See "Surgical management of gallbladder cancer", section on 'Cross-sectional imaging'.)

The role of PET with fluorodeoxyglucose (FDG) in patients with GBC is unclear. Most (86 percent) GBCs are FDG avid [118,119], and PET scanning may help to distinguish between benign and malignant gallbladder wall thickening found on US, CT, or MRI [120-123]. However, while some data suggest that PET predicts residual disease in the local tumor bed in over 80 percent of patients who had a recent previous cholecystectomy and were found to have an incidental GBC [118,119], the temptation to use FDG-PET to determine the need for reresection should be tempered by the frequent finding of increased FDG-PET activity in the local tumor bed as a common early postoperative change [118,119] and the high rate of residual disease, even in incidentally discovered T1 disease (12 percent) [124].

The main utility of PET is in identifying otherwise radiographically occult advanced disease in order to avoid unnecessary surgery. In retrospective studies, preoperative PET scanning changed stage and treatment in approximately 17 to 23 percent of patients with an apparently localized, potentially resectable GBC [118,123,125]. However, others document a low sensitivity for extrahepatic disease in this setting (50 percent), particularly for identifying peritoneal carcinomatosis [119].

The available data are insufficient to make conclusive statements about the clinical utility of PET or integrated PET/CT in the management of patients with GBC [126]. Nevertheless, most institutions do not pursue PET or PET/CT prior to resection of a GBC, given the relative insensitivity for small peritoneal metastases, or prior to reresection following a prior cholecystectomy, because of the difficulty in distinguishing between FDG-avid inflammation and FDG-avid cancer.

Laboratory studies — Laboratory studies are generally nondiagnostic; an elevated alkaline phosphatase or serum bilirubin may be related to bile duct obstruction. Serum tumor markers such as carcinoembryonic antigen (CEA) or carbohydrate antigen 19-9 (CA 19-9, also called cancer antigen 19-9) are often elevated, but they are not diagnostically useful because they lack specificity and sensitivity [127,128]. Nevertheless, if a tumor marker is found to be elevated preoperatively, serial assay after resection might aid in the diagnosis of persistent or recurrent disease.

STAGING

Several staging systems have been used for GBC. Although the staging system developed by Nevin was previously used in Europe [129], the Tumor, Node, Metastasis (TNM) staging system of the combined American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) is now the preferred classification scheme [102].

TNM staging system — The current version (eighth edition) of the AJCC/UICC staging system is outlined in the table (table 3) [130]. The 2017 staging system differs from the earlier 2010 version in a number of ways:

- T2 disease is now subdivided into two groups according to location: T2 tumors on the peritoneal side of the gallbladder are T2a, while those on the hepatic side are T2b. The reason for this stratification is that tumors on the hepatic side have a poorer prognosis, with higher rates of vascular invasion, neural invasion, and nodal metastases, than those arising on the peritoneal side [131]. In this multicenter report of 252 patients with resected

T2 GBC, five-year survival rates for tumors on the peritoneal and hepatic side were 65 versus 43 percent.

- The N classification has changed from a location-based to a number-based assessment. N1 is one to three positive nodes, while N2 disease is four or more positive nodes. There is also a recommendation that six or more nodes be harvested and evaluated. This change was based on studies that demonstrated that the number of metastatic lymph nodes and the lymph node ratio are more prognostic than the location of the metastatic lymph nodes [132-135]. The regional nodes include those along the common bile duct, hepatic artery, portal vein, and cystic duct. Nodes that are beyond the hepatoduodenal ligament (including periaortic, pericaval, superior mesenteric artery, and celiac artery lymph nodes) are extraregional and staged as distant metastases (M1 disease).

These changes in the classification of GBC have improved the prognostic stratification of the staging system. Observed survival rates from a multicenter series of 437 cases of GBC stratified according to stage grouping are depicted in the figure (figure 1) [131].

Stage distribution at presentation — The primary T stage distribution (as defined by the 2010 seventh edition classification) in a contemporary series of 439 cases of incidentally found GBC from a German registry stratified according to the type of surgical procedure is illustrated in the table (table 5) [136]. Positive lymph nodes were found in 21 and 44 percent of the resected patients with T2 and T3 tumors, respectively.

The stage distribution from a multicenter contemporary series of 437 cases of resected GBC stratified according to the 2017 T stage definitions was as follows [131]:

- T1 – 11 percent
- T2 – 58 percent (61 percent peritoneal [T2a] and 39 percent hepatic [T2b])
- T3 – 30 percent
- T4 – 2 percent

Positive lymph nodes were found in 17 and 40 percent of the resected patients with peritoneal or hepatic T2 tumors, respectively, and in 59 percent of the T3 tumors.

The most common sites of metastatic disease are the peritoneum and liver. Occasionally, distant metastases affect the lungs and pleura [130].

The mode of presentation impacts the stage distribution and prognosis of GBC [16,93,136]; there are fewer cases of metastatic disease, and outcomes are better for patients whose tumors are discovered incidentally at the time of cholecystectomy and who are deemed candidates for

re-exploration and possible radical resection [16]. (See "Surgical management of gallbladder cancer", section on 'Outcomes'.)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Gallbladder cancer (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Epidemiology, histology, and risk factors**
  - Gallbladder cancer (GBC) is an uncommon but highly fatal malignancy. Worldwide, there is prominent geographic variability in GBC incidence that correlates with the prevalence of cholelithiasis. Incidence steadily increases with age, women are affected two to six times more often than men, and GBC is more common in White compared with Black people. (See 'Epidemiology' above.)
  - The majority (close to 90 percent) are adenocarcinomas, although other histologic types are occasionally found, including adenosquamous or squamous cell carcinoma, small cell neuroendocrine tumors, lymphoma, and sarcoma. (See 'Histology and molecular pathogenesis' above.)
  - Several risk factors have been identified, many of which share a common characteristic of chronic gallbladder inflammation: gallstone disease, gallbladder polyps and

congenital biliary cysts, anomalous pancreaticobiliary junction, and chronic infection. (See 'Risk factors' above.)

- **Clinical presentation and diagnostic evaluation**

  - Patients with early invasive GBC are most often asymptomatic, or they have nonspecific symptoms that mimic or are due to cholelithiasis or cholecystitis. Malignancy diagnosed incidentally on pathologic examination after a simple cholecystectomy is the most common mode of presentation of early stage disease. (See 'Clinical presentation' above.)

  - Since many patients are diagnosed intraoperatively at the time of cholecystectomy for cholelithiasis, an important issue is the screening of patients with symptomatic biliary tract disease for the possibility of coexisting GBC. Ultrasound (US) is typically the initial study; however, the overall accuracy of US for staging the local and distant extent of suspected GBC is limited. (See 'Patients with symptomatic cholelithiasis' above.)

    Additional imaging (typically cross-sectional imaging with computed tomography [CT] or magnetic resonance imaging [MRI]/magnetic resonance cholangiopancreatography [MRCP]) is needed for patients who have concerning findings on US (calcification, a mass protruding into the lumen, loss of interface between gallbladder and liver, direct liver infiltration, gallbladder polyps ≥10 mm, or a thickened gallbladder wall that is not explained by cholecystitis). In this setting, evaluation of potential resectability is the key factor. (See 'Computed tomography and magnetic resonance imaging' above.)

    Cross-sectional imaging is also recommended for patients who are found to have an incidentally diagnosed GBC at the time of simple cholecystectomy. For those with incidentally diagnosed GBC, appropriate imaging and detailed histopathologic analysis are needed to decide whether further resection is necessary. (See 'Suspicious ultrasound findings or incidental gallbladder cancer at cholecystectomy' above.)

  - Cholangiography is of little use for patients suspected of having GBC since the gallbladder is not observed in most cases, except in situations in which GBC cancer is suspected in the setting of jaundice. (See 'Cholangiography' above.)

  - To complete the staging evaluation, consensus-based guidelines from several groups recommend cross-sectional imaging of the chest in patients who appear otherwise to be potential candidates for resection. The available data are insufficient to make conclusive statements about the clinical utility of positron emission tomography (PET)

or integrated PET/CT in the management of patients with GBC. (See 'Completing the staging evaluation' above.)

- Laboratory studies are generally nondiagnostic; an elevated alkaline phosphatase or serum bilirubin may be related to bile duct obstruction. Serum tumor markers such as carcinoembryonic antigen (CEA) or carbohydrate antigen 19-9 (CA 19-9, also called cancer antigen 19-9) are often elevated but are not diagnostically useful because they lack specificity and sensitivity. Nevertheless, if a tumor marker is found to be elevated preoperatively, serial assay after resection might aid in the diagnosis of persistent or recurrent disease.

- **Staging** – Several staging systems have been used for GBC. Although the staging system developed by Nevin is still used, particularly in Europe, the Tumor, Node, Metastasis (TNM) staging system of the combined American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) is the preferred classification scheme in both Europe and the United States. (See 'Staging' above.)

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Topic 2491 Version 34.0

GRAPHICS

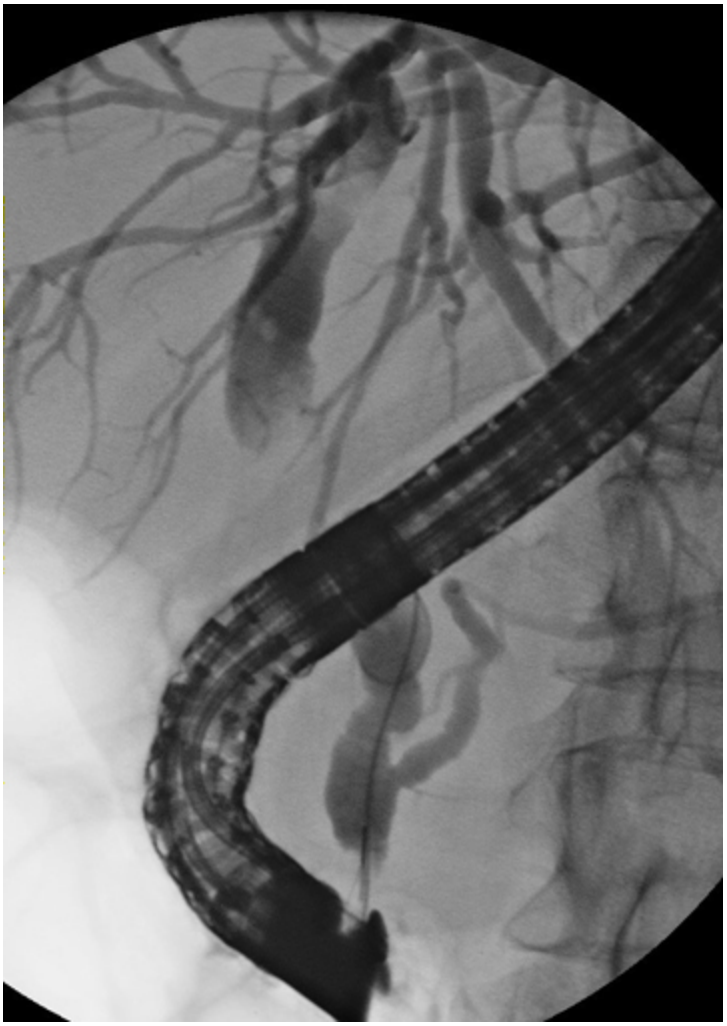
Relative frequency of the different pathologic types of gallbladder polyps

Type	Frequency
Benign polyps	
Cholesterol polyps	60%
Adenomyomas	25%
Inflammatory polyps	10%
Adenomas	4%
Miscellaneous:	1%
Leiomyomas	
Fibromas	
Lipomas, etc	
Malignant polyps	
Adenocarcinoma	80%
Miscellaneous:	20%
Mucinous cystadenomas	
Squamous cell carcinoma	
Adenoacanthomas	

Data from: Weedon, D. Benign mucosal polyps. In pathology of the gallbladder, Mason, New York 1984. p.195. and Laitio, M, Pathol Res Pract 1983; 178:57.

Graphic 56347 Version 2.0

Abnormal pancreaticobiliary junction



Endoscopic retrograde cholangiopancreatography in an adult with obstructive jaundice demonstrates an abnormal pancreaticobiliary junction with a malignant biliary stricture replacing the cystic duct insertion. There is no evidence of a biliary cyst.

Courtesy of Mark D Topazian, MD.

Graphic 57937 Version 4.0

Common histologic types of gallbladder cancer

Tumor type*	Percent of total
Adenocarcinoma	76
Papillary	6
Mucinous	5

Adenosquamous	4
Squamous	2
Oat cell	0.5
Nonspecified	8

* Data collected from 3038 patients treated between 1977 and 1986. Two-year survival for papillary type was 47%. For tumors limited to the gallbladder, five-year survival was 32%.

Modified from Henson, DE. Cancer 1992; 70:713.

Graphic 76301 Version 2.0

Gallbladder cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor invades the lamina propria or muscular layer
T1a	Tumor invades the lamina propria
T1b	Tumor invades the muscular layer
T2	Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum). Or tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver.
T2a	Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum)
T2b	Tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the 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 the main portal vein or hepatic artery or invades two or more extrahepatic organs or structures
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases to one or three regional lymph nodes
N2	Metastases to four or more regional lymph nodes
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis
Prognostic stage groups	

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1	N0	M0	I
T2a	N0	M0	IIA
T2b	N0	M0	IIB
T3	N0	M0	IIIA
T1-3	N1	M0	IIIB
T4	N0-1	M0	IVA
Any T	N2	M0	IVB
Any T	Any N	M1	IVB

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 110890 Version 8.0

Endoscopic ultrasonography for the differential diagnosis of polypoid gallbladder lesions

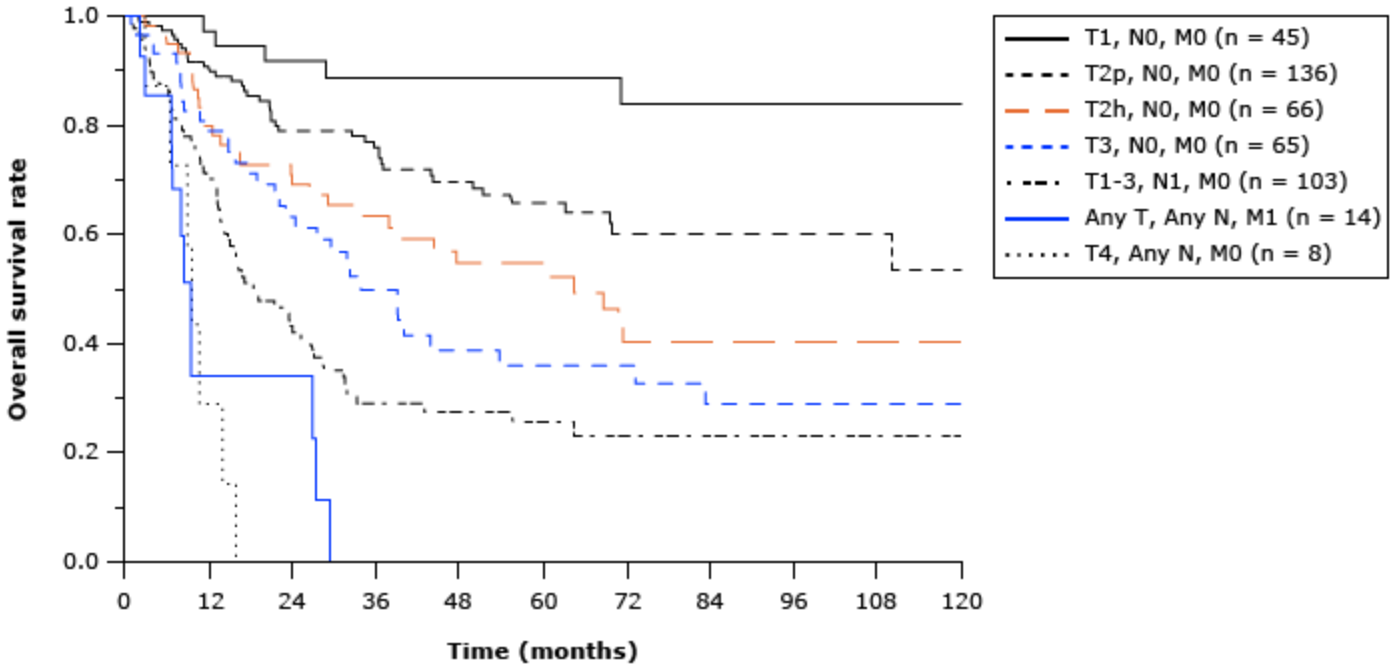
	Number of patients	Histologic diagnosis		
		Cholesterol polyp	Adenomyomatosis	Neoplastic
Preoperative diagnosis with endoscopic US				
Cholesterol polyp	34	34	0	0
Adenomyomatosis	7	0	7	0
Neoplastic	17	2	0	15
Preoperative diagnosis with transabdominal US				
Cholesterol polyp	24	24	0	0
Adenomymatosis	5	0	5	0
Neoplastic	29	12	2	15

US: ultrasound.

Data from: Sugiyama, M, Xie, XY, Atomi, Y, Saito, M, Ann Surg 1999; 229:498.

Graphic 52861 Version 2.0

Survival after resection of gallbladder cancer, stratified by stage according to t 2017 TNM staging criteria



Comparison of survival according to conventional TNM classification with subclassification of T2 tumors by tumor location. N factor and M factor were clinically determined on the basis of either histopathologic findings or radiographic evaluation.

TNM: tumor, node, metastasis.

Graphic 110891 Version 5.0

Stage distribution for 439 incidentally found gallbladder cancers in a German registry, according to type of surgery performed

Pathologic T (tumor) stage	Laparoscopic, percent (n = 239)	Open resection, percent (n = 131)	Conversion from laparoscopic to open resection* (n = 69)
pTis	5	2	1
pT1	21	21	19
pT2	56	38	24
pT3	12	19	46
pT4	4	15	7
pTx	3	5	3

* Conversion to an open procedure for non-oncologic reasons.

Data from: Goetze TO, Paolucci V. Benefits of reoperation of T2 and more advanced incidental gallbladder carcinoma: analysis of the German registry. Ann Surg 2008; 247:104.

Graphic 71493 Version 4.0

Contributor Disclosures

Bhoomi Mehrotra, MD No relevant financial relationship(s) with ineligible companies to disclose. **Kenneth K Tanabe, MD** Patent Holder: EGF SNP to determine risk for HCC [Cirrhosis, hepatocellular carcinoma]; Use of EGFR inhibitors to prevent HCC [Cirrhosis, hepatocellular carcinoma]. Consultant/Advisory Boards: Cancer Expert Now [GI cancers, melanoma]; GSK [GI Cancers]; Imvax [GI cancers]; Leidos [Melanoma, GI cancers]; Teledoc [GI cancers, melanoma]. Other Financial Interest: American Cancer Society [Honoraria as editor of Cancer]. All of the relevant financial relationships listed have been mitigated. **Christopher G Willett, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Sonali M Shah, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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