

# Diagnosis and Management of Gallbladder Cancer

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## Abstract

Gallbladder cancer (GBC) is a rather uncommon disease, but at the time when it gives symptoms it has usually reached no longer curable stage. Therefore, all attempts must be made to make the diagnosis earlier to have better opportunity for cure. The author searched PubMed, and reviewed literatures on diagnoses and treatment of GBC.

**Keywords:** Diagnosis, Gallbladder cancer, Incidence, Metastases, Risk factors, Staging, Treatment

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## Introduction

Since the first description of the gallbladder carcinoma by Maxmillan de Stol in 1777, studies have established a characteristic pattern of late diagnosis and ineffective treatment of this disease.<sup>[1]</sup> Gallbladder cancer (GBC) can be clinically obvious, an unexpected finding at laparotomy, detected incidentally on histologic examination or may be missed only to present with recurrence during follow-up.<sup>[2]</sup> GBC is characterized by local invasion, extensive regional lymph node metastasis, vascular encasement, and distant metastases. In general, GBC is the most aggressive of the biliary cancers with the shortest median survival duration.

Resection is the most effective and only potentially curative treatment. Early-stage tumors are often curable with a proper resection; however, many patients present late in the course of the disease when surgical intervention is no longer effective.<sup>[3]</sup> Patients with unresectable or metastatic GBC have a poor prognosis. In patients with suspected GBC, an open surgical resection is advocated. Adjuvant combination chemotherapy and molecular targeted therapy are emerging as effective therapeutic

options in those with advanced GBC. Endoscopic palliation of biliary and gastric outlet obstruction with metallic stents has improved the quality of life.<sup>[4,5]</sup>

In this article, by searching the publications on PubMed, the author has summarized the current status and key issues in the diagnosis and management of GBC, and hopes to improve diagnosis, treatment, and survival of patients with GBC.

## Risk factors of gallbladder cancer

Many factors are associated with the development of GBC. The routine histopathology examination of the gallbladder, particularly in cases of empyema and patient's older than 60 years, is of value for identifying unsuspected conditions requiring further postoperative management.<sup>[6]</sup> The risk of GBC is increased in anomalous pancreaticobiliary duct junction, gall stones, xanthogranulomatus cholecystitis, calcified or porcelain gallbladder, cholelithiasis with typhoid carriers, gallbladder adenoma, red meat consumption, and tobacco uses.<sup>[7]</sup> Predisposing risk factors for GBC include cholelithiasis, chronic biliary infections (*Opisthorchis viverrini*, *Salmonella typhi*), primary sclerosing cholangitis (PSC), and porcelain gallbladder.<sup>[8-10]</sup> The presence of large gallstone is also one of the major risk factors. A stone size of more than 3 cm, a family history of GBC, and the duration of cholelithiasis are potential risk factors for developing GBC.<sup>[9,11]</sup>

Gallbladder polyps are associated with a risk of malignancy.<sup>[12]</sup> Choledochal cysts,<sup>[13]</sup> porcelain gallbladder, and chronic gallbladder infection

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10.4103/1947-2714.98586

has been implicated as a risk factor for malignant degeneration.<sup>[11,14-17]</sup> Pancreaticobiliary maljunction is a risk factor for GBC and bile duct cancer.<sup>[11,18,19]</sup> PSC is a risk factor for cholangiocarcinoma.<sup>[20-22]</sup> Patients with PSC often develop advanced cholangiocarcinoma with a poor prognosis. In patients with PSC, therefore, strict follow-up should be recommended. Adenoma and dysplasia have been regarded as precancerous lesions of GBC. A polypoid lesion of the gallbladder that is sessile, has a diameter greater than 10 mm, and/or grows rapidly, is highly likely to be cancerous and should be resected. With respect to ampullary carcinoma, adenoma of the ampulla is considered to be a precancerous lesion.<sup>[11]</sup>

Patients with cholesterosis were less likely to have cancer than those who did not have cholesterosis. Therefore, cholesterosis has a strong negative association with GBC.<sup>[23]</sup> Occult pancreaticobiliary reflux is associated with precancerous mucosal changes in the gallbladder, and can lead to inflammatory changes of the biliary epithelium and progress toward the development of precancerous mucosal changes and GBC.<sup>[24]</sup> Pancreaticobiliary maljunction is associated with an increased frequency of gallbladder malignancy. Intestinal metaplasia is often observed in gallbladder disease and is a risk factor for gallbladder carcinoma in adults. The hyperplasia–dysplasia–carcinoma progression is one of the possible mechanisms involved in biliary carcinogenesis.<sup>[25,26]</sup>

Diabetes is a risk factor for GBC,<sup>[27]</sup> and GBC risk may be reduced by controlling diabetes, stones, and high-density lipoprotein levels.<sup>[28,29]</sup> Certain genetic variants involved in the regulation of obesity-related insulin sensitivity may increase susceptibility to bile duct cancer and gallstones.<sup>[30]</sup> Obesity and overweight are associated with a risk for GBC.<sup>[31-35]</sup> Comparable factors include lifestyle, dietary habits, religion, education, family income, chewing of tobacco, as well as smoking, which play an important role in carcinogenesis.<sup>[36,37]</sup>

### Symptoms and signs of gallbladder carcinoma

The clinical presentation of GBC is often vague or delayed relative to pathologic progression, contributing to advanced staging and dismal prognosis at the time of diagnosis. The clinical presentation is nonspecific, may include abdominal pain, weight loss, fever, and jaundice, and any of these can be seen in cholecystitis and other benign gallbladder conditions as well as in other abdominal malignancies.<sup>[8,38]</sup>

It is important to differentiate at an early stage. Ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) have improved the possibility of differentiating and choosing the correct treatment.<sup>[39]</sup>

Mass occupying lesion may be present in 40%–65% of patients with GBC at initial detection. The presence of a large gallbladder mass that nearly fills or replaces the lumen, often directly invading the surrounding liver parenchyma, is highly suggestive of GBC.<sup>[8]</sup> GBC may present as focal or diffuse asymmetric wall thickening, which can have an expansive differential diagnosis, including acute and chronic cholecystitis, xanthogranulomatous cholecystitis, and adenomyomatosis, as well as diffuse hepatic or systemic diseases, such as acute hepatitis, portal hypertension, and congestive heart failure. Conventional cross-sectional imaging may be limited in differentiating gallbladder carcinoma from chronic cholecystitis; however, at contrast-enhanced CT and MRI, diffuse symmetric wall thickening suggests a nonneoplastic process, whereas asymmetric, irregular, or extensive thickening, which may have marked enhancement during the arterial phase that persists or becomes isodense or isointense to the liver during the portal venous phase should heighten suspicion of GBC. GBC may arise as a nidus in pre-existing background chronic cholecystitis, which can obscure or delay the diagnosis of cancer.<sup>[8]</sup>

### Acute cholecystitis

GBC may manifest as acute cholecystitis. For elderly patients, especially women, presenting with acute cholecystitis and abnormal liver function, CT demonstration of focal gallbladder wall thickening, intraluminal masses, small gallbladder with diffuse wall thickening, and enlarged regional lymph nodes are suggestive of concurrent GBC.<sup>[40,41]</sup>

### Acute lithiasic cholecystitis

GBC may present as acute lithiasic cholecystitis that leads to severe septic complications. Severe septic complications in elderly patients with a long-standing history of gallbladder stones may coexist with primary carcinoma of the gallbladder.<sup>[42]</sup>

### Mirizzi syndrome

Mirizzi syndrome has a low incidence in patients with gallbladder disease. The coexistence of GBC seems to be more frequent in patients with Mirizzi syndrome than in those with gallstones only.<sup>[43]</sup> There were no clinical features to differentiate these patients with GBC from those with Mirizzi syndrome alone, except that they were a decade older and had longer duration of symptoms. The diagnosis of GBC was made on final histology after cholecystectomy.<sup>[44,45]</sup>

### Other diseases

GBC presenting as gallstone ileus,<sup>[46]</sup> gallbladder perforation,<sup>[47]</sup> duodenal ulcer,<sup>[48]</sup> gastroduodenal

dysmotility,<sup>[49]</sup> malnutrition,<sup>[50]</sup> venous thromboembolism,<sup>[51]</sup> gynecologic symptoms,<sup>[52]</sup> skin disorders,<sup>[53]</sup> paraneoplastic symptoms,<sup>[54]</sup> and even neuropathy<sup>[55]</sup> have been reported.

## Diagnostics and Staging

In the diagnosis of GBC, differential diagnosis and determination of the local extension of tumor are important. For these purposes, imaging modalities such as endoscopic ultrasonography (EUS), CT, MRI, and magnetic resonance cholangiopancreatography (MRCP) are useful. EUS has good sensitivity in differentiating benign gallbladder diseases from GBC.<sup>[56]</sup>

Most of the gallbladder tumors are benign. Adenoma, cholesterol polyps, or adenomyomatosis are most frequently typical on ultrasonographic images. It may be difficult to identify precancerous or malignant lesion. All symptomatic lesions must be considered as indications for surgery. Polyps over 1 cm are indication for preventive cholecystectomy. In case of suspicious polyp or suspicious wall thickening, EUS can be helpful to evaluate local tumoral spread and eliminate differential diagnosis. CT and MRI examinations are useful for local and metastatic staging.<sup>[57]</sup>

### Ultrasound image studies

Ultrasonography (US), a useful initial modality when exploring the background of jaundice or nonspecific gastrointestinal complaints, sensitively reveals bile duct obstruction in particular.<sup>[58,59]</sup> In unclear cases, or if US suggests a resectable biliary malignancy, CT, MRI with magnetic resonance cholangiography (MRC) and/or traditional cholangiography often provide additional information, and imaging-guided fine-needle biopsy or an endoscopic brush sample may verify the malignant nature of the tumor.<sup>[60]</sup> Complementary modalities are usually needed for accurate staging, and traditional cholangiography is often performed for therapeutic purposes as well.<sup>[61]</sup>

The poor prognosis of GBC is related to its dissemination capacity and usually late diagnosis due to its nonspecific clinical appearance. The first step in an early diagnosis is to identify patients in the appropriate epidemiologic setting (eg, incidental finding, chronic cholecystitis) for the correct interpretation of test results. It is desirable to enhance the sensitivity of the initial US examination by use of the appropriate technology in skilled specialist hands. When GBC is suggested by US findings, fluorodeoxyglucose-positron emission tomography (FDG-PET) can be considered complementary to establish the benign/malignant nature of the lesion and to obtain a primary staging study. If GBC

is confirmed, thin-slice spiral CT can contribute valuable information on local spread.<sup>[56,62,63]</sup> Although CT is inferior to ultrasound in depicting mucosal irregularity, mural thickening, and cholelithiasis, it is superior for evaluating the thickness of portions of the gallbladder wall that are obscured by gallstones or mural calcification on ultrasound. CT may show focal or irregular mural thickening; the images should be carefully inspected for bile duct dilation, local invasion, metastases, and adenopathy.<sup>[8,59]</sup> Recent hybrid PET-CT systems provide structural and functional information simultaneously, and may offer early and accurate staging with an improved specificity.<sup>[64-69]</sup>

On MRI, GBC usually shows hypo- to isointense signal characteristics. An all-in-one protocol supplementing MRI with cholangiographic (MR cholangiopancreatography) and contrast-enhanced arterial and portal phase 3D angiographic (MR angiography) images may be up to 100% sensitive for bile duct and vascular invasion, yet sensitivity falls to 67% for hepatic invasion and 56% for lymph node metastases.<sup>[8]</sup> Dynamic MRI with MRCP is an accurate and a reliable method of showing GBC and in assessing its local and regional extent as part of preoperative assessment.<sup>[70]</sup>

### Cytology

A carcinoma at early stages can be overlooked, and the diagnosis would then be made only after microscopic examination of paraffin-embedded tissue. Imprint cytology of the gallbladder mucosa is an easy, rapid, and high-quality method for detecting GBC.<sup>[71]</sup> Ultrasound-guided fine-needle aspiration cytology is also a safe diagnostic modality for GBC.<sup>[72]</sup> Endoscopic retrograde cholangiopancreatography of biliary tree and GBC is highly specific and should be considered for evaluation of clinically suspicious lesions.<sup>[73]</sup>

### Tumor markers

Tumor markers have an increasing significance in the diagnosis and evaluation of GBC. Assay of CA242, CA15-3, CA19-9, and CA 125 are fairly good markers for discriminating patients of carcinoma of the gallbladder from cholelithiasis. CA242 and CA125 when used together achieved best sensitivity and specificity. Serum markers seem to be less sensitive when used individually in carcinoma of the gallbladder but may prove useful in combination.<sup>[74]</sup>

### Electrophoretic pattern of proteins

Electrophoretic analysis of serum protein has revealed protein bands in patients with carcinoma of the gallbladder as compared with electrophoretic pattern in cholelithiasis.<sup>[75]</sup>



## Gallbladder membrane lipids

Fourier transform infrared (FTIR) spectroscopy is sensitive to the molecular composition of tissue, and has the potential to identify premalignant tissue. Lipids were increased in the plasma membrane during carcinogenesis of the gallbladder; the ratio of intensity could be a marker to diagnose cancer by FTIR.<sup>[76]</sup>

## Surgical Technical Aspects

GBC is characterized as an aggressive and highly lethal disease, and surgery is the only option for the treatment.<sup>[77]</sup> A more aggressive surgical approach, including resection of the gallbladder, liver, and regional lymph nodes, is advisable for patients with T1b to T4 tumors. Aggressive resection is necessary because a patient's GBC stage determines the outcome, not the surgery itself. Therefore, major resections should be offered to appropriately selected patients. Patients with advanced tumors or metastatic disease are not candidates for radical resection and thus should be directed to more suitable palliation.<sup>[78,79]</sup>

Complete surgical resection remains the only potentially curative treatment for primary adenocarcinoma of the gallbladder. Several basic concepts of surgical management of this illness are straightforward, whereas others remain controversial. Aggressive surgical therapy of GBC is becoming more common as large institutional series demonstrate longer survival times from more extensive resections.<sup>[80]</sup> Long-term survival is possible in early stage of gallbladder carcinoma. Surgery for gallbladder carcinoma has the potential to be curative only in local or regional disease.<sup>[81,82]</sup>

## Today's recommended routine surgery

The majority of patients present with advanced-stage tumors (stage IV), and are not amenable to surgical resection. A small percentage of patients present with stage I disease, and may be cured by cholecystectomy. The role for surgery in patients with stage II and III disease remains controversial, but most hepatobiliary surgeons believe that an aggressive surgical approach improves survival for these patients. However, the extent of hepatic and lymph node resection, the need for resection of the extrahepatic ducts in nonjaundiced patients, the role of vascular resection, and the advisability of hepatopancreatoduodenectomy remain a matter of debate. Although no data from prospective, randomized studies are available, resection of the gallbladder and adjacent liver with or without the extrahepatic bile ducts and with a regional lymph node dissection is the operative approach recommended for selected patients with GBC.<sup>[83]</sup>

For patients with T1b, T2, and T3 incidental GBC, re-resection is generally recommended. At re-exploration, many patients with incidental GBC will have residual disease. Definitive oncologic management requires re-resection of the liver, portal lymphadenectomy, and attention to the common bile duct. The extent of the hepatic resection should be dictated by the ability to achieve a microscopically negative (R0) margin. Routine resection of the common bile duct is unnecessary, but should be undertaken in the setting of a positive cystic duct margin.<sup>[84]</sup>

In patients with a preoperative diagnosis of GBC, it is imperative that the patient be treated with a cholecystectomy with en-bloc hepatic resection with lymphadenectomy with or without bile duct resection. The extent of the hepatic resection varies from a wedge of the gallbladder bed to major right lobe of liver resections.<sup>[85]</sup> The rationale for including a bile duct resection should be based on the cause of the GBC, with routine excision of the bile duct performed for patients with anomalous pancreatic bile duct junctions. The excision of the bile duct should be performed only when involved or when surgically indicated.<sup>[85]</sup>

## Prophylactic cholecystectomy

Since there is a strong association between long-standing gallstone disease and the development of GBC, a study from India has indicated that prophylactic cholecystectomy is recommended in populations with high incidence of GBC.<sup>[86]</sup> Data from the West, however, indicate that the risk of GBC in persons with asymptomatic gallstone is very small and does not warrant prophylactic cholecystectomy. Not all persons with asymptomatic GS require cholecystectomy. Type of stone, tumor markers, and genetic markers need to be investigated to identify those with asymptomatic GS who are at the highest risk of developing GBC so that they can selectively be offered pre-emptive cholecystectomy to prevent GBC.<sup>[87]</sup>

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**How to cite this article:** Andrén-Sandberg Å. Diagnosis and management of gallbladder cancer. *North Am J Med Sci* 2012;4:293-9.

**Source of Support:** Nil. **Conflict of Interest:** None declared.