



Management of Gallbladder Carcinoma

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Last few decades have seen changes in the approach toward the management of gallbladder cancer (GBCA). Availability of high-definition imaging modalities and accurate interpretations of their findings have helped in early and accurate diagnosis. A structured approach toward the disease with the aid of clinical, noninterventional/interventional radiology and laparoscopic findings has helped surgeons to choose between an aggressive approach of radical cholecystectomy for those with a resectable growth and suitable palliation for those who are unlikely to benefit from therapeutic laparotomy, thereby helping in proper and judicious utilization of health-care resources. Better understanding of the tumor biology is encouraging oncologists for trials with different targeted therapies in advanced disease. This review addresses some of the key issues related to the management of GBCA based on extensive search of available literatures and current international guidelines.

Key words: Gallbladder cancer, diagnosis, staging, management

INTRODUCTION

Gallbladder cancer (GBCA) is the fifth most common type of gastrointestinal malignancy and is the most common malignancy of the biliary tract. It is an uncommon cancer in the West, with an estimated incidence and mortality in the US of 11,420 and 3710, respectively, in 2016.¹ However, it is one of the common and lethal malignancies encountered in women of North and Central India, showing an increasing trend among both genders in northern and eastern parts of India.^{2,3} It is still a difficult entity to treat, especially when the patient presents with a large tumor. Due to its late presentation, it was traditionally associated with a poor prognosis as is evident from what Alfred Blalock wrote in 1924, “in malignancy of the gallbladder (GB), when the diagnosis can be made without exploration, no operation should be performed, inasmuch as it only shortens the patient’s life.”⁴

The scenario has undergone a sea change over the last nine decades. The sense of despondency and nihilism has given way to greater interest and hope for treating the disease, mostly in view of early diagnosis, better understanding of the etiopathogenesis, advances in the imaging, widespread acceptance of laparoscopic cholecystectomy, more experience

with major liver resections, and wider availability of interventional techniques for palliating symptoms of advanced disease. Long-term survival has now been reported following radical resection of large tumors invading the liver and also in patients who had previously undergone noncurative exploration.⁵

The key to better outcome is of course early diagnosis, accurate staging, and appropriate surgical intervention.

The present review is written in this backdrop, incorporating the currently available guidelines regarding the management of this dreaded disease.

DIAGNOSIS AND STAGING

Patients with GBCA may present to a clinician in either of the following ways: as an incidental histopathological finding following cholecystectomy done for chronic cholecystitis, incidental unexpected finding during surgery, GB mass detected preoperatively on imaging, and advanced cases with clinically apparent GB mass and jaundice. Some patients, in whom the diagnosis was missed during the initial histopathology, may present with locally recurrent tumor.

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The management of GBCA is primarily surgical. The nature of surgery depends on the stage of the disease at diagnosis. The earlier the disease is diagnosed and its resectability established, the better is the prognosis. Nearly 70% of the cases in the US are diagnosed incidentally, either intraoperatively or on the postoperative pathology; the remaining 30% are diagnosed preoperatively on cross-sectional abdominal imaging done for nonspecific symptoms such as right upper quadrant abdominal pain mimicking cholecystitis, nausea, vomiting, weight loss, or jaundice.⁶⁻⁹

While patients of GBCA detected incidentally are more likely to be in the early stages, those diagnosed preoperatively, especially with the ominous sign of jaundice, ascites, or abdominal mass are mostly in an advanced and inoperable stage.^{5,10}

The primary imaging modality for the assessment of presumed benign GB disease is an ultrasonography (USG). Although it has an accuracy of more than 80% in diagnosing GBCA, it is not an useful tool for staging the disease.^{6,11}

Cross-sectional imaging of GBCA has three broad patterns. Most commonly, a hypoechoic (relative to liver) mass obscuring the GB lumen which shows increased flow on color doppler with or without infiltration into the adjacent liver, an intraluminal polypoidal mass >1 cm in size, having a broad base and fixed to the wall (a sludge ball or blood clot with similar sonographic findings will move), or focal wall thickening and irregularity.^{6,11} Focal or diffuse thickening of GB wall, the least common presentation of GBCA, is best appreciated on USG though it requires an expert radiologist. Marked and irregular wall thickening is a feature of advanced disease.^{6,12}

One-fourth of the cases of GBCA presents as a polypoidal mass projecting into the GB lumen. These lesions are most likely to be limited to the GB mucosa and muscular layer and therefore picking them up early is prognostically important.¹³ USG can occasionally detect liver metastases/invasion, biliary or portal vein involvement, and enlarged lymph nodes.¹²

Gallstones are a common association being present in 75%–92% of cases, and those with stone size >3 cm have ten times more risk of GBCA than those with stones <1 cm.^{12,14,15} Although gallstone disease is prevalent in 10%–15% of adult population, only 0.5% of these patients develop GBCA over 20 years.¹⁶ GBCA occurring in the absence of stones has been associated with anomalous pancreatic bile duct junctions, chronic inflammatory bowel disease, and primary sclerosing cholangitis.

Porcelain GB is not associated with an increased risk of GBCA as is the popular belief.^{15,17} Selective mucosal calcification, rather than diffuse intramural calcification, may be more closely associated with GBCA.¹⁷

An USG finding which is significantly common in GBCA is the discontinuity of the mucosal echo in association with a solitary stone within GB.¹⁸ Contrast-enhanced ultrasound has been evaluated in the characterization of GB lesions, though its potential remains to be clearly defined.¹⁹

Conventional transabdominal USG cannot assess the depth of invasion or T-stage, which directly correlates with the prognosis.^{6,20} It has also little role in N and M staging of the disease.

However, endoscopic USG (EUS) can visualize in detail the layers of GB wall and has a diagnostic accuracy of 100%, 75.6%, 85.3%, and 92.7% for pTis, pT1, pT2, and pT3-4 growths, respectively.¹³ Moreover, the scope for EUS in the management of GBCA is likely to expand with time as more expertise are gained with interventional EUS, especially preoperative EUS-guided fine-needle aspiration cytology (FNAC) from intraaortocaval (IAC) lymph nodes to detect metastasis, for avoiding nontherapeutic laparotomy.²¹

Contrast-enhanced computed tomography (CECT) is far superior to USG in the assessment of the N- and M-stages and also in the involvement of adjacent structures. It helps in isolating patients who might benefit from surgical resection.^{6,8,20} CECT typically shows asymmetric wall thickening with marked enhancement during the arterial phase, which becomes isodense to liver during portal venous phase. CT is inferior to USG for detecting thickening and irregularity of GB wall and also cholelithiasis. However, it can evaluate portions of GB wall overlapped with stones or mural calcification better than USG.^{22,23}

Polypoidal cancer appears denser than the surrounding bile and enhances homogeneously with administration of contrast.

Magnetic resonance cholangio-pancreaticography (MRCP) and MR angiography are useful tools for determining resectability in patients where the biliary tree and major vessels are suspected to be involved.^{6,24}

The role of fluorodeoxyglucose-positron emission tomography (FDG-PET) is still evolving. Its greatest advantage is that a larger area can be scanned with smaller radiation dose. In patients with incidental finding of carcinoma following cholecystectomy, PET-CT is useful in detecting local residual disease in GB fossa and nodal and distant metastases. It is also useful in postoperative follow-up to detect any recurrence.²⁵

TREATMENT

The only potentially curative therapy for GBCA is surgical resection. The depth of tumor invasion or the T-stage is

the most important factor which determines the extent of surgical resection and also the prognosis. Broadly speaking, T1 and T2 tumors are limited to the GB wall, while T3 and T4 have extended beyond it. N1 lymph nodes are limited to the hepatoduodenal ligament and stage wise are potentially resectable, while patients having N2 disease are considered to have metastatic disease (M1). Other than the lymph nodes, the peritoneum and the liver are the other common sites of distant metastases. There is a direct correlation between the T-stage and the incidence of nodal and distant metastases.^{6,20} Stage wise, I and II are resectable with curative intent, Stage III is locally advanced and entails major resection, and Stage IV is unresectable because of distant hematogenous or lymphatic metastases, peritoneal implants, or invasion of major vessels such as celiac, superior mesenteric artery, aorta, or vena cava. Pathological diagnosis is required before any nonsurgical therapy, but it is not essential for patients with characteristic findings of resectable GBCA.

ROLE OF STAGING LAPAROSCOPY

The extensive workup for patients of GBCA is to identify and segregate those with advanced disease who are unlikely to benefit from therapeutic laparotomy. Staging laparoscopy (SL) along with laparoscopic USG complements preoperative imaging in detecting metastases on liver surface, peritoneum, or IAC lymph nodes, thereby obviating nontherapeutic laparotomy in up to 48% of cases.^{26,27}

APPROACH TO PATIENTS WITH PREOPERATIVE DIAGNOSIS

Patients who after workup and SL, are found to have no metastatic disease are subjected to laparotomy. Perioperative confirmation of the SL findings is followed by sampling of IAC lymph nodes from below the level of left renal vein and its frozen section biopsy. If it is found to be negative, one proceeds for the radical surgery; otherwise, an attempt is made for a suitable palliation.

The only treatment of potentially curative intent in GBCA is an aggressive R0 resection.²⁸ Aggressive surgery entails radical cholecystectomy, which includes adequate lymphadenectomy and adequate liver resection along with *en bloc* resection of any involved viscera.

Adequate lymphadenectomy means clearance of the lymph nodes and fibro fatty tissue in the hepatoduodenal ligament to the extent that bile duct and vessels therein are skeletonized; the hepatic artery is bared of nodes till its origin from celiac axis. Nodes anterior and posterior to the head of pancreas are also cleared.³

Adequate liver resection, for no liver involvement (T1b and T2 tumors), entails either an *en bloc* resection of the GB along with a 2-cm nonanatomical wedge of liver (when this is done along with adequate lymphadenectomy, it is termed as extended cholecystectomy) or a formal anatomical bisegmental liver resection (segments IVb/V). T3/T4 tumors with extensive liver infiltration or GB neck tumors with vascular or major bile duct involvement would require a right hepatectomy/right trisegmentectomy (Couinaud's segments 4, 5, 6, 7, and 8) if hepatic reserve is adequate.²⁸⁻³¹

Anomalous pancreatic bile duct junctions and positive cystic duct stump on frozen section are indications for bile duct excision.³¹

APPROACH TO PATIENTS WITH INCIDENTAL DIAGNOSIS

Incidental GBCA encompasses patients who are diagnosed to be having GBCA either during cholecystectomy or on pathological review of the GB. Its incidence ranges from 0.5% to 2.1%.^{15,18} In a series from Japan, its incidence is 27%–41% of all GBCAs.³² When the operating surgeon unexpectedly comes across a suspected malignant GB during laparoscopic cholecystectomy, he/she can either convert it to an open procedure and do a formal extended cholecystectomy if he/she has the expertise or abort the procedure without any attempt of resection or biopsy and refer the patient at the earliest to a hepatobiliary surgeon with the necessary technical expertise, thereby facilitating the first resection to be a definitive one and avoiding the harms of peritoneal/port-site dissemination or noncurative resection.

On the other hand, when a patient presents to a hepatobiliary surgeon with pathology report of GBCA detected after a previous simple cholecystectomy, the T-stage of the lesion will aid him/her in selecting patients who would benefit from radical re-resection.

For Tis and T1a tumors with negative resection margins and cystic node, the cure rate is 85%–100% without any further intervention.³³ They need close follow-up radiologically and testing of carcinoembryonic antigen and CA19-9.

T1a tumors with positive nodes and T1b tumors need re-exploration for adequate lymphadenectomy along with excision of segments IVb and V of liver (with a curative intent as well as for adequate staging) with or without bile duct excision depending on whether the cystic duct stump is positive or not. The 1-year survival drops down to only 50% for T1b tumors not undergoing radical excision.³⁴ The patient must be counseled about the possibility of no residual disease in the resected specimen.

One-third of the patients with T2 tumors will have regional lymphadenopathy.^{5,34} The same is true for >50% of patients with T3 tumors.³⁵ Hence, cases with T2 disease must have a CECT to look for any residual disease or lymphadenopathy and those with T3 and above, a FDG-PET is preferable for the same. If there is no evidence of N2/M1 disease and the patient has an adequate liver reserve, he/she would benefit from a R0 resection including an anatomical bisegmental liver resection or a right/extended right hepatectomy, regional lymphadenectomy, and resection of adjacent involved structures with or without bile duct excision depending on the positivity of cystic duct margin.^{36,37} Radical R0 resection for T2 tumors is associated with 5-year survival of more than 80%, while the same for T3 tumors is 21%.^{5,38} On an average, 74% of the patients show residual disease on re-exploration and the median survival is far better (72 months) for patients who have no evidence of disease as compared to those with residual disease.³⁹

T4 diseases are rarely confused as benign GB disease, carry a dismal prognosis (5-year survival in the range of 0%–5%), and are seldom resectable.¹⁵ Fluoropyrimidine-based chemoradiotherapy or gemcitabine chemotherapy (CT) alone may be considered in patients with adequate performance status and intact organ function as adjuvant treatment for T4 and also T3 and N2 (unresectable, recurrent, or metastatic) diseases.^{40,41}

Postoperative adjuvant gemcitabine and platinum-based CT and external beam radiotherapy should be offered to patients with poorly differentiated, aggressive T2, or higher, node/margin-positive lesions.⁴²

Intensity-modulated radiation therapy is the newer technical advancement which allows highly conformal radiation delivery, sparing as far as possible the normal organs.⁴³

Some believes that radical re-resection, if not otherwise contraindicated by the patient's status, may still be beneficial in terms of long-term survival even for T4 disease.⁵

Full-thickness excision of all port sites during completion-extended cholecystectomy is recommended by some though there is no consensus in this regard as many also believe that this procedure is only of staging/prognostic significance and gives no survival benefit; most patients with microscopic deposits on the excised port sites later presented with peritoneal recurrence.^{5,44}

APPROACH TO PATIENTS WITH UNRESECTABLE/METASTATIC DISEASE

The National Comprehensive Cancer Network makes the following recommendations:

- Enrollment for clinical trials

- Fluoropyrimidine or gemcitabine chemotherapy
- Supportive care: Percutaneous or endoscopic endobiliary or gastrointestinal stents for relieving jaundice or duodenal obstruction, narcotics for pain relief
- Palliation for patients with jaundice before instituting chemotherapy.

EUS/CT-guided fine-needle aspiration biopsy for establishment of pathological diagnosis is required before institution of palliative nonsurgical therapy.⁴⁵

NOVEL THERAPIES

GB carcinoma has been associated with the mutations of KRAS, INK4a, p53 genes, and amplification of human epidermal growth factor receptor (EGFR), (HER)-2/Neu.⁴⁶ Human EGFR mutations have also been identified. Targeted therapies may either prevent ligand binding and activation of EGFR or compete with ATP binding to tyrosine kinase domain, blocking downstream signal transduction, thereby affecting cellular activities such as transcription, differentiation, and apoptosis.

It is likely that a particular population of patients of GBCA with EGFR mutations/overexpression might respond favorably to EGFR inhibitors as encouraging results have been documented with inhibitors such as gefitinib in patients of non-small cell lung cancers and pancreatic cancers with EGFR mutations.⁴⁷ A Phase II study with a single agent erlotinib on patients with biliary tract cancers has shown promising results.⁴⁸ Another randomized Phase II trial on patients of advanced cholangiocarcinoma and GBCA suggested the efficacy of cetuximab followed by gemcitabine plus oxaliplatin.⁴⁹

Similarly, vascular endothelial growth factor expression has been correlated with advanced and metastatic GBCA. Bevacizumab and sorafenib were tested, with promising results, in multicentric Phase II trials in unresectable and metastatic cases of GBCA.^{50,51}

The 8th edition of American joint committee on cancer (AJCC) staging system for gallbladder carcinoma is given in Table 1.⁵² The T2 category is separated into T2a (stage IIA) and T2b (stage IIB), based on tumor location on the peritoneal and hepatic sides of the gallbladder, respectively. This change is based on a recent study, demonstrating worse survival for tumors on the hepatic side of the gallbladder.⁵³

The N category has been uniformly changed for gallbladder, perihilar bile ducts, distal bile duct, ampulla, and pancreas. N1 is defined as one to three metastatic lymph nodes, and N2 as four or more metastatic lymph nodes. A number-based categorization of metastatic lymph nodes results in better prognostic stratification.

Table 1: American Joint Committee On Cancer staging system for gallbladder carcinoma⁵²

T - primary tumor	
TX	Primary cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma <i>in situ</i>
T1a	Tumor invades lamina propria
T1b	Tumor invades muscle layer
T2a	Tumor invades perimuscular connective tissue on the peritoneal side without serosal involvement
T2b	Tumor invades perimuscular connective tissue on the hepatic side (without hepatic involvement) or both hepatic and peritoneal sides
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as stomach, duodenum, colon or pancreas, omentum or extrahepatic bile ducts
T4	Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures
N-regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases to one to three regional lymph nodes
N2	Metastases to four or more regional lymph nodes
M-distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Tumor staging	
Stage 0	Tis N0 M0
Stage I	T1 N0 M0
Stage II A	T2a N0 M0
Stage II B	T2b N0 M0
Stage IIIA	T3 N0 M0
Stage IIIB	T1-T3 N1 M0
Stage IVA	T4 N0-1 M0
Stage IVB	Any T N2 M0 Any T Any N M1

CONCLUSION

GBCA, if not resected, is rapidly fatal. Most Tis and T1a tumors are discovered incidentally following laparoscopic cholecystectomy and require no further treatment. Infiltration beyond T1a requires aggressive radical surgery for long-term survival. Adjuvant chemoradiotherapy for selective patients can be beneficial. Ongoing trials are suggesting that a subgroup of patients of GBCA with advanced and metastatic diseases might benefit from targeted therapies.

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Conflicts of interest

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