



# Management of gallbladder cancer in India

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**Abstract:** Gallbladder cancer is a highly aggressive disease with variable prevalence across the globe. Particularly the Indo-Gangetic belt in Northern India has an incidence as high as 21/100,000. Majority of cases are detected either incidentally on pathological evaluation of cholecystectomy specimens or present with advanced disease. Radical surgery remains the mainstay of cure but only a small subset of patients is operable at presentation, and even with curative surgery recurrence rates remain high. Much debate surrounds the management of gallbladder cancer, with continuously evolving standards regarding the extent of hepatic resection and lymphadenectomy, curative resection in patients presenting with jaundice, routine excision of bile duct, and the role of neoadjuvant chemoradiotherapy. In this review we present a synopsis of currently available evidence and emerging approaches in the management of gallbladder cancer in India.

**Keywords:** Gallbladder cancer; incidental gallbladder cancer; locally advanced gallbladder cancer; port site excision; revision cholecystectomy; Tata Memorial Hospital criteria (TMH criteria)

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## Introduction

Gallbladder cancer is the most common cancer of the biliary tract, with incidence and prevalence that is highly variable across different regions of the world. The Indo-Gangetic belt in Northern India is one of the highest affected regions with an incidence of about 21/100,000. It has one of the shortest median survivals from the time of diagnosis, reflecting its aggressive behaviour and late stage of diagnosis (1). Radical surgery, which is the only chance for cure, is possible in only about 10% of the cases at presentation. Moreover, even in patients with curative surgery, recurrence rates remain high.

Gallbladder cancer usually presents in one of the following three ways: diagnosed malignancy (commonly advanced disease), malignancy detected intraoperatively for cholecystectomy done for an apparently benign disease, and malignancy diagnosed incidentally on

pathologic examination following routine cholecystectomy. Approximately two-thirds of cases of gallbladder cancer are diagnosed during surgery or post-operatively (2). In patients who are symptomatic, symptoms are usually non-specific with right upper quadrant pain being the most common symptom followed by jaundice. Among patients suspected to have Mirizzi syndrome, 6–27.8% of patients will have a final diagnosis of gallbladder cancer, the probability being higher in patients having elevated CA19.9 levels (3).

There has been much debate regarding the principles of management of gallbladder cancer. Controversy still surrounds regarding the management of T1b disease, extent of hepatic resection and lymphadenectomy, resection of port sites, curative resection in patients presenting with jaundice, routine excision of bile duct and whether surgical strategy differs between pT2 tumors according to tumor location.

## Management of early gallbladder carcinoma (operable)

Early gallbladder cancer is suspected preoperatively in only 30–40% on imaging and the majority of them are detected incidentally on histopathological examination. For Tis and T1a lesions a simple cholecystectomy with negative cystic duct margins is sufficient and is associated with a cure rate of 85–100% (4). Gallbladder lesions with T staging T1b and above are associated with a significant incidence of nodal metastases and therefore require radical resection, which includes en bloc hepatic bed resection (2–3 cm of liver wedge or formal segment IVb and V resection) with periportal lymphadenectomy. Cystic duct margin should be negative, and if positive, should be followed by revision of duct margin or extrahepatic bile duct excision.

### Preoperative work-up

Majority of patients detected as gallbladder cancer have only an ultra-sonogram as the preoperative imaging. Since gallbladder cancer is an aggressive disease with a high incidence of unresectability and metastatic disease a detailed preoperative work-up is mandatory prior to planning a curative resection. High resolution cross-sectional imaging is essential for adequate staging. A good imaging would avoid un-necessary laparotomies in patients with advanced disease who would otherwise not be candidates for curative resection (5). Both contrast enhanced computed tomography (CECT) and magnetic resonance imaging (MRI) are helpful in identifying metastatic disease, as well as defining the extent of primary lesion. Positron emission tomography (PET)-CT scan may help detecting metastatic disease which is occult on CT scan. However, PET scan has significant false positive results and therefore histological confirmation of metastases should always be considered before denying a patient curative surgery. Staging laparoscopy has high accuracy for detecting peritoneal and liver surface metastases and should be performed in patients who are non-metastatic on imaging. In a study by Agarwal *et al.* (5) staging laparoscopy obviated a non-therapeutic laparotomy in 23% of gallbladder cancer patients. Based on this they recommended a routine staging laparoscopy in patients with gallbladder cancer with no evidence of metastatic disease on preoperative work-up.

### Pre-operative tissue diagnosis

Pathologic tissue diagnosis is unnecessary in patients where

the tumor is considered resectable. In unresectable patients planned for neoadjuvant or definitive chemotherapy, percutaneous biopsy is a reliable method of diagnosis with a sensitivity of approximately 88% (6). Removing the gallbladder in an attempt to provide a pathologic diagnosis is not advised in view of significant risk of tumor spillage.

### Principles of surgery

The goal of surgery is R0 resection. There are two basic components of a curative surgery: resection of gallbladder mass and liver, and clearance of locoregional lymph nodes. Over the years much has been described regarding the “ideal” surgical approach in gallbladder cancer.

### Extent of liver resection

There has been much controversy regarding the extent of liver resection, whether anatomical segment IVb and V resection is better as compared to non-anatomical wedge excision of liver. Of recent, there has been a shift towards parenchyma-sparing surgeries. A study from Memorial Sloan-Kettering Cancer Centre (MSK) (7) showed that performance of a major hepatectomy was not associated with long-term survival but, instead, was associated with increased perioperative morbidity. In another study by Pawlik *et al.* (8) there was similar risk of disease-specific death among patients who underwent a major hepatic resection (e.g., formal segmentectomy of 4b and 5 or hemihepatectomy) and patients who underwent a hepatic wedge resection. Similar results were reported by other authors (9). It was shown that surgical margin status was the key determinant of overall outcome, and not the type of liver resection (10). Therefore, the goal of surgeon should be to remove all disease with negative histologic margins. A major hepatectomy may occasionally be required for adequate tumor clearance and an R0 resection in tumors involving hepatic inflow vascular structures.

pT2 tumors have been subdivided in the 8th edition of AJCC according to the epicentre of tumor: pT2a are those involving the peritoneal side and pT2b are those involving the hepatic side. According to Shindoh *et al.* (11) T2a gallbladder cancer was associated with a good prognosis compared with T2b gallbladder cancer. In a study by Lee *et al.* (12) hepatic resection was an important factor associated with overall survival in patients with hepatic-side gallbladder cancer, but not in peritoneal side gallbladder cancer. This may be attributed to the anatomic differences in drainage routes between T2a and T2b gallbladder cancer.

A more recent study has shown that hepatic resection had no significant treatment effect in T2 gallbladder cancer patients (13); however, the results were not of statistical significance. Based on these facts it would be advised to consider hepatic resection in T2 gallbladder cancer till further recommendations.

### Lymphadenectomy

The standard lymphadenectomy for gallbladder cancer includes nodes along the common hepatic artery, hepatoduodenal ligament and retropancreatic region (stations 8, 12 and 13 respectively). Extended “radical” lymphadenectomy of non-regional nodes (including celiac, peripancreatic, periduodenal, and superior mesenteric lymph nodes) is not routinely advocated (14-16). Disease spread to celiac and para-aortic lymph nodes is considered metastatic disease, and surgical resection is contraindicated. Thus, during laparotomy, after ruling out disseminated disease, the first attempt should be to do a Kocher manoeuvre to evaluate aortocaval nodes. Suspicious interaortocaval nodes should be evaluated intra-operatively with frozen pathologic assessment, and, if positive, the procedure should be abandoned at that time. At least six lymph nodes should be removed during surgery for accurate staging (17). It would be worth mentioning here that the highest peri-pancreatic lymph node marks the transition between the regional and non-regional fields, and has been shown to be of prognostic importance in biliary tract adenocarcinoma (18).

### Role of routine excision of bile duct

Few authors have advocated routine resection of common bile duct during resection stating that this facilitates lymphadenectomy and increases lymph node yield (19). However, this belief has been challenged by others (7,10), and has also shown to be associated with increased morbidity (7). Rather, the decision to consider bile duct resection depends on the status of cystic duct margin. A positive cystic duct margin has an incidence of residual disease in the common bile duct of 42%, whereas, it is only 4% for those patients who had a negative cystic duct margin (8). Therefore, evaluation of cystic duct margin status, with an intra-operative frozen pathological assessment if needed, should be a routine step in curative surgery, and if found positive, a bile duct resection should be performed to achieve R0 resection. Also, bile duct excision may be necessary to achieve complete nodal clearance where nodes are densely adherent and their removal risks injury to bile duct.

### Minimally invasive surgery for gallbladder cancer

With the increasing use of minimally invasive techniques (laparoscopy and robotic surgery) it is natural for a procedure like radical cholecystectomy to be attempted via these techniques. Initial studies had reported an increase in the incidence of port-site recurrence due to the manipulation of instruments through ports, and also due to the chimney effect associated with pneumoperitoneum (20,21). Recent studies (22-24), however, have failed to demonstrate any significant detrimental effect of minimal invasive radical cholecystectomy, with few studies showing improvement in blood loss and length of hospital stay (25,26). Minimally invasive radical cholecystectomy can be attempted provided the expertise is available and without compromising the oncological safety of the procedure. Use of retrieval bags and avoiding bile spillage are of utmost importance.

### Incidental gallbladder cancer

Incidental gallbladder cancer is defined as gallbladder cancer suspected for the first-time during cholecystectomy or detected on pathological examination of the gallbladder after removal for presumed benign disease (27). Incidental gallbladder cancer is found in approximately 0.2–1.1% of all laparoscopic cholecystectomies (28). The incidence of finding residual disease at any site depends on the pathological T stage of tumor. This incidence can be as high as 37.5% in T1 tumours, 56.7% in T2 tumours, and 77.3% in T3 tumours (8). Incidence of residual disease in the liver bed and/or lymph nodes is relatively low, ranging from 12% in patients with T1 tumours to 46% in those with T3 tumours. Even though there are no prospective clinical trials, it has been suggested that complete resection of residual disease is associated with improved survival. Several studies have demonstrated survival advantage with curative resection, thus supporting re-resection in incidental gallbladder cancer (29-31).

### *Selecting patients for re-resection: who will benefit?*

Not all patients referred to a tertiary centre with a diagnosis of incidental gallbladder cancer need revision surgery. For T1a tumors with negative cystic duct margin, a simple cholecystectomy is sufficient and no additional resection is required (4) since it does not provide any additional survival

**Table 1** Incidence of residual disease and LN involvement in IGBC

T stage	Residual disease	LN metastases	Risk of recurrence
pT1b	10%	10–20%	20–50%
pT2	10–30%	31%	40%
pT3	36%	46%	–

benefit. For tumors staging T1b and above residual disease and lymph nodal metastases is significant, and a revision surgery is warranted (32) (Table 1). Relevant intra-operative findings which also tilt the decision towards consideration for revision surgery include incomplete removal of gallbladder and specimen retrieval without using bag. Gallbladder perforation and bile spillage has been shown to be associated with increased rates of recurrence (33) and decreased disease-free and overall survival (34).

#### *Time-interval for revision surgery*

Few authors (35) have advocated a deliberate delaying of restaging for incidental gallbladder cancer in order to permit careful evaluation for residual disease and extrahepatic spread, as well as observation of the biologic behavior of the tumor. Proponents of this concept believe that this strategy avoids unnecessary laparotomies in patients who may not have benefited from surgical resection, without adversely affecting survival in patients who remained candidates for resection. On the contrary, interval to re-resection has been shown by few authors to be a poor prognostic indicator (36). In a study by Barreto *et al.* (37) it was shown that the risk of recurrence does not depend on the delay of the radical re-resection following simple cholecystectomy, but rather on the disease stage per se. Based on their findings they have recommended that revision surgery should be performed irrespective of time interval from primary surgery as long as the disease is non-metastatic on preoperative work-up.

#### *PET-CT*

The role of <sup>18</sup>F-fluorodeoxyglucose (FDG) PET scan in incidental gallbladder cancer is still debatable. Considering the relative high risk of metastatic disease, a PET scan can alter the management in a significant number of cases. In one study (38) specifically looking at the role of PET scan in incidental gallbladder cancer, both PET-CT and MDCT had complementary roles which together increased the likelihood of detecting previously occult metastatic disease.

Another study by Goel *et al.* (39) recommended PET-CT as a useful adjunct in treatment planning in patients with incidental gallbladder cancer where they showed that PET-CT could significantly alter the management of pT1b patients. PET-CT may be falsely positive in cases of incidental gallbladder cancer secondary to inflammation in gallbladder fossa. To minimise this PET-CT should be advised 4–6 weeks after the initial surgery. Summing it up, FDG-PET should not be used to determine whether re-resection is warranted for residual disease. Instead, FDG-PET may be helpful to identify occult distant metastatic disease in those patients who are otherwise being considered for revision surgery.

#### **Role of staging laparoscopy**

Staging laparoscopy in patients with incidental gallbladder cancer has a low yield of approximately 14% (40) and may be unwarranted according to few, especially because the peritoneum should have already been examined during index surgery. However, there is a subgroup of patients where the yield of staging laparoscopy is high, and these include patients with high T-stage, a positive pathologic margin and high tumour grade (40). However, since staging laparoscopy does not significantly increase the overall operative time and may reduce the hospital stay and expenses if patients are found to have advanced/unresectable disease it should always be considered in these high-risk group patients.

#### *Port site excision*

In majority of instances when incidental gallbladder cancer is detected the primary surgery has been a laparoscopic cholecystectomy. Of late it has been proposed that port site metastasis is a harbinger of peritoneal carcinomatosis. In a study from MSK (41) and another by Fuks and colleagues (42), port-site resection was not associated with overall survival or recurrence-free survival. As such, routine resection of port sites during re-resection is not mandatory

and is no longer recommended.

In an instance where gallbladder cancer is detected intraoperatively, either on initial laparoscopy or on cut-opening the gallbladder on the back table, an attempt should be made to perform a complete staging. Whether to proceed with a more definitive oncologic surgery or to abort the procedure and refer the patient to a specialized hepatobiliary center depends on skill-set of the surgeon and available logistics. Long-term survival is similar among patients managed with immediate versus staged re-resection for gallbladder cancers (43), and therefore, surgeons unfamiliar with complex hepatobiliary procedures should refer such patients to a hepatobiliary center without the concern for adversely affecting the patient's prognosis.

### Management of locally advanced gallbladder cancer

Locally advanced gallbladder cancer comprises a tumor which perforates the serosa and/or directly invades the liver or one adjacent organ (T3), or a tumor which invades main portal vein or hepatic artery or two or more extrahepatic organs (T4), with or without regional lymph node metastasis.

#### *Jaundice as presenting symptom*

Patients with symptomatic gallbladder cancer have significantly worse survival as compared to patients with incidental gallbladder cancer, even when matched stage to stage (8). Symptomatic patients with gallbladder cancer usually present with jaundice or a right hypochondrial mass. The presence of jaundice suggests malignant invasion of the biliary tree and majority will have disseminated disease. The median disease specific survival among jaundiced patients with gallbladder cancer is only 6 months (44). These patients usually require resection of common bile duct and are associated with positive margins in almost 40% cases (45). However, in a study by Nundy *et al.* (46), curative resection with negative margins was possible in 50% cases of gallbladder cancer patients presenting with jaundice. In view of these contrasting results, gallbladder cancer patients presenting with jaundice should not be denied a curative resection, rather a meticulous evaluation for resectability should be considered. Endoscopic or percutaneous biliary drainage coupled with neoadjuvant chemotherapy should be considered in such patients with an aim to achieve better disease control.

#### *Extent of surgical resection*

The principles of surgery for locally advanced gallbladder cancer remain essentially the same as for early gallbladder cancer, including liver resection and lymphadenectomy. However, an R0 resection in this case may include a major or extended hepatectomy, bile duct resection and reconstruction, and resection of adjacent organs (stomach, hepatic flexure of colon). In cases of T4 disease, the peri-operative morbidity and mortality associated with extensive reconstructions generally outweigh any survival benefit, and therefore extensive resection and vascular reconstruction is usually not recommended. Neoadjuvant therapy should be considered in these cases. Considering the high risk of metastatic disease in symptomatic gallbladder cancer cases, a staging laparoscopy should always be done before proceeding for radical resection. It has been shown that staging laparoscopy can prevent futile laparotomy in 38% to 62% of patients with additional detection of N2 disease with the help of intraoperative ultrasound (5,38).

#### *Role of neoadjuvant therapy*

Surgical resection offers the only potential cure for gallbladder cancer, and since a large number of patients present with locally advanced gallbladder cancer, down-staging these patients with neoadjuvant therapy can increase the number of patients undergoing curative surgery. Another benefit of neoadjuvant treatment would be to evaluate the biology of the disease and identify the candidates who would benefit the most from surgery. The best candidates for neoadjuvant therapy would be patients with T3/T4 tumors and/or node-positive disease who are predisposed to high chances of recurrence despite radical surgery. Goel *et al.* proposed the Tata Memorial Hospital (TMH) criteria (47) (*Table 2*) as an indication for chemotherapy with neoadjuvant intent in locally advanced/borderline resectable gallbladder cancer, which resulted in curative surgical resection or disease stabilization in a significant proportion of patients. Initial studies had shown no benefit of neoadjuvant therapy in patients who were operated with negative margins (48). However, few series have demonstrated a benefit of gemcitabine-platinum based neoadjuvant therapy in gallbladder cancer (49-51). Investigators at Tata Memorial Hospital (Mumbai, India) are conducting one such prospective trial, POLCA-GB (52), which aims to compare chemotherapy alone (four cycles of gemcitabine-cisplatin

**Table 2** TMH criteria (for locally advanced/borderline resectable GBC used as an indication for neoadjuvant chemotherapy)

Tumour (T3–T4 tumours)
<ul style="list-style-type: none"> <li>• Contiguous liver involvement &gt;2 cm</li> <li>• Involvement of bile duct causing obstructive jaundice (type I/II block on MRCP/ERCP/PTBD)</li> <li>• Radiological/Endoscopic involvement of antropyloric region of stomach, duodenum, hepatic flexure of colon or small intestine</li> </ul>
Node (N1 station)
Radiological suspicion of lymph node involvement N1
<ul style="list-style-type: none"> <li>• Hepatic artery (station 8),</li> <li>• Hepatoduodenal ligament (station 12),</li> <li>• Retro pancreatic/retroduodenal (station 13)</li> </ul>
Size >1 cm in short axis, round in shape, and heterogenous enhancement on CT/PET scan
Vascular (T4 tumours)
Impingement/involvement (<180 degrees) of one or more of the following blood vessels:
<ul style="list-style-type: none"> <li>• Common hepatic artery and right &amp; left hepatic artery</li> <li>• Main portal vein and right &amp; left portal vein</li> </ul>
For incidental GBC
<ul style="list-style-type: none"> <li>• Residual/recurrent mass in GB fossa/liver bed</li> <li>• N1 nodes as per nodal criteria</li> <li>• Involvement of bile duct causing obstructive jaundice (type I/II block)</li> </ul>

PET, positron emission tomography; CT, computed tomography; GBC, gallbladder cancer; TMH, Tata Memorial Hospital.

or gemcitabine-oxaliplatin) versus chemoradiotherapy (RT concurrent with gemcitabine) followed by chemotherapy (two cycles of gemcitabine-cisplatin or gemcitabine-oxaliplatin) with the goal being to downstage locally advanced gallbladder cancer and permit potentially curative resection. This trial is currently in the recruitment phase.

### Adjuvant therapy in resected gallbladder cancer

Recommendations regarding adjuvant chemotherapy are largely based on the results of two trials. The PRODIGE 12-ACCORD 18 (UNICANCER GI) trial evaluated adjuvant gemcitabine and oxaliplatin versus surveillance in patients with resected localized biliary tract cancer and found no benefit of adjuvant chemotherapy (53). However, the BILCAP trial evaluating adjuvant single-agent capecitabine versus observation in operated biliary tract cancers showed a significantly improved survival with adjuvant chemotherapy (54). Few recent meta-analyses also suggest a benefit for adjuvant chemotherapy, maximally in patients with R+ resections, lymph node positivity, and Stage II and above disease (55–57). Based on these observations, adjuvant chemotherapy is currently recommended for T1b and above disease and node-positive disease.

### Adjuvant chemoradiotherapy in resected gallbladder cancer

Till date, there are no randomized studies establishing the role of adjuvant radiotherapy or chemoradiotherapy in resected gallbladder cancer. The single-arm SWOG S0809 phase II trial, which evaluated the role of chemotherapy (gemcitabine-capecitabine) and chemoradiotherapy with capecitabine in patients with resected biliary tract cancers has shown good outcomes with adjuvant chemoradiotherapy (58). A meta-analysis by Horgan *et al.* (55) showed a benefit with chemoradiotherapy, especially in patients with R+ resections or node-positive disease. Even though adjuvant radiotherapy alone has shown benefit in gallbladder cancer (59), considering the benefits of chemotherapy, it would be prudent to offer adjuvant chemoradiotherapy in patients with positive margins or node-positive disease (60,61). For patients with node-positive disease and negative resection margins, there is insufficient evidence at present to choose between adjuvant chemotherapy and chemoradiation. In the absence of clear evidence, many experts will treat node-positive, margin-negative patients with adjuvant chemotherapy followed by consolidative chemoradiotherapy after restaging confirms an absence of distant metastases. Adjuvant chemoradiation may be

recommended in patients with positive resection margins.

### Recurrence in gallbladder cancer

Despite best attempts at curative resection, recurrence rates remain high, with the risk of recurrence being higher in symptomatic cases as compared to incidental gallbladder cancer. Jarnagin *et al.* (62) reported a recurrence rate of 66% after curative resection for gallbladder cancer, with majority having distant metastases, thereby representing poor tumor biology and systemic failure. The only factor associated with distant recurrence is positive resection margins, thus highlighting the importance of R0 resection in the definitive treatment of gallbladder cancer. Recurrent gallbladder cancer is usually unresectable, and treatment options are usually limited to symptom relief. Chemotherapy may be offered to patients with good performance status, and radiotherapy can be an option in patients with non-regional recurrence and who have not received prior radiation therapy.

### Management of metastatic gallbladder cancer

A biopsy to confirm the diagnosis is recommended in patients with unresectable or metastatic disease. The current standard of care for advanced gallbladder cancer is palliative chemotherapy using a gemcitabine-based doublet, with cisplatin or oxaliplatin commonly being the accompanying drug (63). This is based on the seminal ABC-02 and BT-22 trials which compared gemcitabine-cisplatin to gemcitabine, and the trial from All India Institute of Medical Sciences (AIIMS), New Delhi, India, which compared gemcitabine-oxaliplatin to 5-fluorouracil and best supportive care (64-66). Patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 to 2 may be considered for single-agent gemcitabine, while patients with ECOG PS 3 or 4 may be considered for palliative care alone. All patients with advanced disease should have access to palliative care along with ongoing chemotherapy. Biliary drainage is an appropriate palliative procedure and should be considered before instituting chemotherapy if possible. Patients progressing on first-line chemotherapy have a poor prognosis. However, in patients with good PS second line chemotherapy may be considered (67,68). Commonly used regimens include 5-FU or capecitabine monotherapy, or combination of capecitabine/5-FU with oxaliplatin and irinotecan. Of recent, use of targeted therapy represents a promising strategy for advanced gallbladder cancer.

Epidermal growth factor receptor (EGFR) inhibitors like erlotinib and cetuximab have been investigated in the Phase II setting in this disease and the results have been encouraging, however, further studies are awaited before standard-of-care recommendations can be entered (69,70).

### Follow-up protocol

No definite protocol has been recommended for follow-up of patients with resected gallbladder cancer, and it is largely institution based. However, strict adherence to follow up is advised in order to detect early recurrences, if any. A 3-monthly follow-up for the initial 2 years after surgery, followed by 6 monthly visits for the next 3 years and annual visits thereafter is advised. Each follow up visit should include a physical examination, serum CA19-9 levels, liver function tests and ultrasonogram of abdomen and pelvis. Any suspicious imaging or biochemical parameter should be evaluated further with a contrast enhanced CT scan or MRI.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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