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Review Article

Incidental gallbladder cancer and its contemporary management: From evaluation to targeted therapy

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ABSTRACT

Gall bladder cancer (GBC) is the commonest malignancy of biliary tract. It is locally aggressive and potentially fatal in most of the patients. With the rise in the number of laparoscopic cholecystectomies being performed worldwide, incidental presentation of GBC is becoming common. The revelation of cancer for benign cholecystectomy presents a challenge. Incidental GBC needs detailed evaluation that includes review of preoperative imaging, histopathology report of cholecystectomy and high quality imaging to look for residual or metastatic disease. It is imperative to correctly stage the disease to formulate the best treatment strategy. For assessment of disease, triple-phase Contrast Enhanced Computed Tomography (CECT) scan and staging laparoscopy have definite roles; with Positron Emission Tomography and Computed Tomography (PET/CT) useful in confirming suspicious lesions. The factors associated with poor prognosis is presence of residual disease, lymphovascular invasion, grade of tumor and presence of metastatic lymph nodes. Neoadjuvant chemotherapy can be employed for the patients who are not candidate for upfront re-resection. Surgery includes liver excision and lymphadenectomy. Adjuvant therapy is indicated for higher stage tumor for improving survival, but response rate is low. Evaluation of biomarkers can provide a target for novel therapy.

Keywords: Incidental Gallbladder cancer; Re-resection; Adjuvant therapy; Targeted therapy

INTRODUCTION

One of the less common malignancies affecting the gastrointestinal (GI) system is gallbladder cancer (GBC). However, it accounts for 80–95% of cancers in the biliary tract.[1,2] The malignancy is aggressive and potentially fatal, with five year survival rates of 5–20% and a mean overall survival of six months.[1,3] Its incidence varies widely with geographical location; being highest in northern India, Pakistan, and Chile.[4,5] In up to 70% of patients, the diagnosis is made incidentally post-cholecystectomy for presumed benign conditions.[6,7] The rest of the patients present with symptoms of abdominal pain, nausea/vomiting, anorexia, weight loss, and jaundice, where the presence of ascites, Gastrointestinal (GI) bleeding, and palpable mass indicate advanced disease and a poor prognosis.[8] It is the only GI malignancy which is more common among women, with mean age of diagnosis in seventh decade.[9,10]

The incidence of GBC has risen in the past two decades, which is in consonance with the rising number of laparoscopic cholecystectomies. The finding of malignancy for benign cholecystectomy poses a challenge to the surgeon, as well as causes distress to the patient; although the prognosis remains favorable than those presenting with symptoms or signs of cancer; as the former group has a less advanced T stage and a lower tumor grade.[11] As per the literature, incidental GBC (IGBC) is associated with solitary and larger gallstone and essentially focal gallbladder wall thickening.[12] There is a lot of debate whether all cholecystectomy specimen

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should be sent for routine histopathological examination. However, studies have shown that routine histopathological examination detects more GBCs than selective examination, but some studies advocate both approaches.[13–15]

DIAGNOSIS AND STAGING

GBC tends to metastasize to lymph nodes, liver, peritoneum, and lungs; therefore, accurate staging must be performed once an IGBC is detected. It includes a detailed assessment of the specimen for depth of invasion, cystic duct margin, and presence of lymph node metastasis, if any. Thereafter, high-quality cross-sectional imaging must be performed to evaluate any residual disease. The investigations include triple phase computed tomography (CT) of the chest, abdomen, and pelvis or liver protocol magnetic resonance imaging (MRI).

The CT scan of the abdomen most accurately helps to evaluate involvement of the liver (local or metastatic), non-regional lymph nodes, vascular invasion (hepatic arteries/ portal vein), invasion of adjacent organs (bile ducts/ duodenum/ colon), and peritoneal spread.[16] Pleural and pulmonary metastases can be ruled out with a CT scan of the chest. Liver parenchyma and bile ducts are best assessed with MRI along with vascular invasion and regional lymph nodes.[17]

Fluorodeoxyglucose (FDG) - Positron Emission Tomography (PET) has good sensitivity for evaluating residual or recurrent disease; however, it does not lead to change in the management significantly.[18] Therefore, routine addition of PET scan is not advisable, especially with pT1a disease; as the utility in finding additional disease or confirming equivocal findings of CT scan are significantly less in IGBC.[19] It should be used selectively if the suspicion of non-regional or distant disease is present on CT/MRI or the stage is pT1b or greater.[20]

Staging laparoscopy is recommended for all patients with GBC > pT1b before performing therapeutic laparotomy, as the invasion into adjacent structures and involvement of regional lymph nodes may not be evident on CT/MRI and the rate of positive findings is as high as 23% for liver surface disease and peritoneal deposits.[21] In a study conducted at Memorial Sloan-Kettering Cancer Center (MSKCC), almost half of the 44 analyzed patients had disseminated disease at laparoscopy.[22] Staging laparoscopy is therefore recommended for all cases of suspected or proven GBC to reduce the incidence of non-therapeutic laparotomies.[23] Laparoscopic ultrasound can be employed whenever available; to look for deeper lesions, the relationship of the tumor with blood vessels, and the feasibility of achieving adequate margins.

ROLE OF NEOADJUVANT CHEMOTHERAPY (SELECTING THE ADEQUATE TREATMENT SEQUENCE)

It is well known that GBC is an aggressive malignancy, and there is a high risk of distant recurrence after curative surgery. This reflects the systemic nature of disease and the requirement for multi-modality treatment. A series has reported a favorable response rate for R0 resection (74.1%) and improved median disease-free survival after neoadjuvant chemotherapy in patients with residual disease after cholecystectomy as well as GBC with a higher stage.[24] This approach not only allows the selection of patients for surgery, as the ones who progress on chemotherapy can be spared the morbidities of major hepato-biliary resection; but also treats micro-metastatic disease. Such high-risk patients can be identified with stage T3 disease, node positivity, poor differentiation, and residual disease as seen with positive margins on cholecystectomy specimens or imaging. However, this strategy must be carefully chosen as the response rate in GBC is around 23% with gemcitabine and platinum doublet[25] and it risks local progression of disease and impairment of the functional status of the patient who is otherwise fit for surgery. This strategy can also be used as a bridge measure, when surgery is not feasible, such as during COVID-19 pandemic.

Re-resection

The current evidence recommends re-resection for all T1–T3 incidental GBCs except pT1a tumors, as there is a significant improvement in overall survival with R0 resection.[26–28] It is based on the rationale that these stages have a high rate of residual disease, i.e., 54% in T1b/T2 disease and 87% in T3[29] and better survival after re-resection than those who do not undergo surgery.[26] One, three, and five-year survival rates of 76%, 54%, and 41%, respectively were reported for the patients who underwent re-resection, as compared with 52%, 20%, and 15% for those who did not opt for resection. Furthermore, this difference in survival had a significant correlation with T-stage.[26] Re-resection for T1a tumors is unnecessary as there is no overall survival benefit[26,27] and they are cured by the cholecystectomy that has been performed already.[28,29] They can be managed with observation, including serial imaging and tumor markers. Few models have been developed to predict residual or distant disease based on T stage, tumor grade, and other pathological variables such as lymphovascular/ perineural invasion.[30,31] One of the models is depicted in Table 1[31] and this has been validated in a study of 59 patients with IGBC.[32] A recent study published for Enhanced Recovery Pathway (ERP) in GBC resection, which comprised 227 (55.6%) patients with IGBC, showed that a good compliance with ERP leads to statistically significant

Table 1: Gallbladder cancer risk predictive score.

Tumor stage		
Tis/T1a		0
T1b		1
T2		2
T3/T4		3
Grade		
G1		1
G2		2
G3		3
LVI		
Negative		1
Positive		2
PNI		
Negative		1
Positive		2
Total risk (Score)	**Loco-regional residual (%)**	**Distant disease (%)**
Low (3–4)	0	0
Intermediate (5–7)	24	3
High (8–10)	61	32

LVI: Lymphovascular Invasion, PNI: Perineural Invasion

better outcomes in terms of post-operative recovery, length of hospital stay, and major post-operative complications.[33]

The following are the absolute contraindications to resection:

- Liver and peritoneal metastases.
- Malignant ascites.
- Para-aortic, paracaval, superior mesenteric artery, and/or celiac artery lymph nodal involvement by the tumor.
- Hepato-duodenal ligament if involved extensively either directly by tumor or through metastasis in the lymph node.
- If the tumor encases or occludes major vessels (e.g., common hepatic artery or main portal vein).

The timing of re-resection has been found to impact overall survival in a multi-institutional study. The cohort that was operated between four and eight weeks after the initial cholecystectomy in that study, had a significantly higher overall survival than those who were operated less than four weeks or more than eight weeks after the cholecystectomy.[34]

Laparoscopic resection

The feasibility of laparoscopic surgery (resection with lymphadenectomy) has recently been demonstrated in a propensity score matched study of 104 patients with biliary tumors. Out of those, 20 cases had gallbladder cancer. Laparoscopic series resulted in lower blood loss, fewer blood transfusions, shorter length of stay, and lower morbidity. The number of lymph nodes harvested was similar to open procedure.[35] Laparoscopic radical surgery for gallbladder cancer is a feasible option in expert hands.

Extent of resection

T1b tumors – If there are no contraindications for surgery, then extended resection (liver tissue from segments IVb and V) is reasonable. There is a survival advantage over patients who undergo simple cholecystectomy by more than three years.[36]

T2 tumors – The standard of care remains extended resection for both T2a and T2b tumors, although the prognosis is slightly worse for the latter.[37] It is based on the fact that up to 57% of patients have residual disease after simple cholecystectomy.[6]

T3 tumors – These patients should undergo extended cholecystectomy with en-bloc resection of the involved adjacent organs and may require major hepatic resection for clearance. However, the extent of resection does not affect survival but it is the tumor biology and stage that predict the outcome.[38]

T4 tumors – These tumors should be clinically identified during the initial cholecystectomy, hence does not meet the criteria of the IGBC by definition. These are locally unresectable due to the involvement of the portal vein, hepatic artery, or multiple adjacent structures. Curative surgery is mostly unfruitful due to the co-existence of metastatic disease.

Extent of liver resection

Several studies have been conducted to compare the role of major hepatectomy, anatomical resection of contiguous segment IV b and V, or wedge resection with adequate margins.[26,38,39] As per the evidence till now, major hepatic resection did not show any survival advantage and this procedure is associated with increased morbidity. Therefore, these procedures should be pursued in selected patients to achieve an R0 resection.[6]

Role of routine bile duct excision

Similarly, several retrospective studies have shown no survival advantage of routine common bile duct excision, with increased morbidity associated with the procedure.[6,38,40] Even this procedure does not increase the lymph node yield.[41] Therefore, common bile duct excision is recommended in selective cases to achieve R0 resection.

Extent of lymph node dissection

In a 2009 Surveillance, Epidemiology and End Results (SEER) study, which included 4,614 patients with T1b-T3 disease, it

was found that pathological evaluation of even a single lymph node showed significant median overall survival improvement over the patients in whom no lymph node was evaluated. Radical resection had no advantage over cholecystectomy alone without lymph node evaluation.[42] At least six lymph nodes should be dissected and sent for histological evaluation for appropriate risk stratification of the disease, as per a 2011 study by MSKCC.[43] A standard lymph node template for GBC should be limited to lymph nodes in the porta-hepatis region and along the hepato-duodenal ligament (cystic, peri-choledochal, and hilar); as para-aortic lymph node dissection did not show any significant improvement in outcomes.[44]

Management of port-site

The gallbladder cancer is prone to peritoneal metastasis, and there are several reports of port-site metastasis after laparoscopic cholecystectomy. The site of extraction is at higher risk than other port sites and the risk increases with a higher T category. However, a systematic review published recently found that the incidence of port-site involvement has decreased from 18.6% to 10.3% ($p < 0.001$) over the past few decades.[45] There are multiple studies, including multi-centric, that mention that there is no statistically significant benefit of routine port site excision in disease-free survival or overall survival, as shown in Table 2.[46–49]

ADJUVANT THERAPY

Surgery remains the only option for curative therapy in GBC, however, the outcomes are poor for those with T3/ node positive disease even after R0 resection. The pattern of recurrence after resection could be loco-regional or involve distant sites; although it is more common at the latter.[24] The choice of agent for systemic therapy in adjuvant setting is Capecitabine alone or along with Gemcitabine as shown in the Southwest Oncology Group (SWOG) feasibility study.[50] A meta-analysis has published significant improvements in survival with adjuvant chemotherapy when compared with surgery alone, especially with node positive and stage II or higher disease.[51] Although the ABC-02 trial showed the superiority of cisplatin and gemcitabine as compared to gemcitabine alone; the combination of gemcitabine –oxaliplatin was not superior to observation alone in PRODIGE-12 ACCORD-18 trial.[52,53] The phase III BILCAP trial showed clinically important; however statistically insignificant, improvement in overall survival with capecitabine and recommended it as a standard of care following surgery.[54]

Table 2: Overall survival of patients undergoing re-resection. PSE (Port Site Excision)

Reference	Patient undergoing re-resection (n)	Overall Survival PSE vs. No PSE (p value)
Fuks D *et al.*[46]	148	0.37
Ethun CG *et al.*[47]	197	0.07
Maker AV *et al.*[48]	113	0.23

n: number of patients

The role of adjuvant radiation is not well defined for GBC. A retrospective study of 73 patients with GBC showed that there was significantly improved Overall Survival (OS) on multivariate analysis with the administration of adjuvant chemo-radiotherapy (HR 0.30; 95% CI 0.13-0.69; $p = 0.004$).[55]

PROGNOSTIC FACTORS AND OUTCOME

Multiple factors affect the outcome in GBC. The most important of them is an R0 resection. The other factors that contribute significantly are T stage, lymph node involvement, tumor grade, and the presence of Lymphovascular Invasion (LVI) & Perineural Invasion (PNI). In the study of 400 patients, which included both IGBC and non-IGBC, the OS was significantly different between those undergoing R0 and R+ resection (71.0% & 17.6%, $p < 0.0001$) and have N0 and N+ disease (75.1% & 45.7%, $p < 0.0001$).[24] The French cohort study of IGBC demonstrated that 5-year OS was significantly related to T stage: 100% (T1), 62% (T2), 19% (T3 & T4),[26] whereas the results from the United States were 59% (T2), 21% (T3), and 28% (T4), respectively.[56] Other study from China has also demonstrated a similar association between T stage and survival outcome.[57]

The presence of residual disease (RD) at the time of re-resection has been identified as a significant prognostic factor for recurrence as well as survival. In a study of 463 patients with IGBC, the median OS after re-resection was superior in those without RD versus patients with RD ($p < 0.001$).[58,59] Another study also provided similar results with worse OS in the presence of RD at any location, even after R0 resection ($p < 0.003$).[32]

The presence of nodal disease at the time of resection has been a poor prognostic marker in multivariate analysis in many studies. A retrospective analysis of 122 patients revealed that microscopic evaluation of at least six lymph nodes improves risk stratification; with worse recurrence-free & disease-specific survival in node-negative patients who have less than six lymph nodes harvested.[43] In their study, Fong *et al.* concluded 5 year survival of 54%, 16%, and 0 for N0, N1 and N2 - nodal classification of the disease ($p = 0.002$) and a relative risk of 2.8.[56] The study by Wang L *et al.* has shown reduced survival for nodal disease with a hazard ratio of 1.56 (95% CI 1.14–2.14, $p = 0.003$).[57]

Studies have reported worsening histologic grade; the presence of lymphovascular invasion and perineural invasion as markers of poor prognosis. The study by Ethun CG *et al.* obtained p values of 0.012 and 0.007 for the effect of tumor

grade and LVI on overall survival[31] whereas another by Butte JM *et al*. showed p values of 0.0009 and 0.015 for tumor grade and PNI affecting disease-specific survival.[60] A retrospective analysis of 1,649 patients revealed LVI as the strongest predictor of nodal metastasis with an odds ratio of 3.69 [95% CI, (2.74–4.97); $p < .001$] and associated with shortened overall survival for all T stages (pT1b – pT3).[61]

Spillage of bile at index cholecystectomy has also been identified as a poor prognostic factor. It is not uncommon to have bile spill at laparoscopic cholecystectomy (either purposeful decompression or inadvertent spill). It has been reported that the bile spill has an adverse effect on rates of re-resection ($p = 0.013$), development of peritoneal carcinomatosis ($p = 0.028$); distant recurrence ($p = 0.04$), and Disease Free Survival (DFS) (0.038) in a study of 82 patients with IGBC.[62] Recently published study has shown a higher peritoneal disease progression rate and significant median DFS reduction in patients with bile spill.[63]

TARGETED THERAPY

Apart from these prognostic factors, various potential biomarkers have been the topic of study of many recent studies. The most prominent biomarkers among them are the amplification of Human Epidermal growth factor Receptor 2 neu (Her2/neu), overexpression of tumor protein 53 (p53) & Epidermal Growth Factor Receptor (EGFR) and mutations in Kirsten rat sarcoma viral oncogene homologue (KRAS). These biomarkers can help stratify patients with advanced gallbladder cancer as well as a potential molecule for targeted therapy in those with incidental gallbladder cancer that progressed rapidly after surgery.[64] HER2 overexpression, the most studied biomarker, is found in nearly 12–18% of cases, and these patients responded favorably to HER2 directed therapy such as Trastuzumab and Lapatinib.[65] Other forms of targeted therapy, such as EGFR inhibitors, Pembrolizumab,[66] have been studied, but not yet practiced widely.

CONCLUSION

The incidence of IGBC is on the rise due to an increase in laparoscopic cholecystectomy. Care should be taken to minimize bile spill during the index cholecystectomy. A meticulous review of the operative notes and histopathology report (HPR) is required by the surgical oncologist when a patient of IGBC approaches for further treatment. A diligent search for residual disease should be done, and metastatic disease must be excluded before radical surgery is offered to the patient. The patient should be prognosticated based on the final HPR, and adjuvant therapy may be advised. The ideal management of IGBC is in a multi-disciplinary setup with careful planning to achieve the best possible outcome for the patient.

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Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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