Gallbladder Cancer

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Introduction

Gallbladder cancer (GBC) is an adenocarcinoma developing from the gallbladder mucosa. It is a relatively uncommon disease, with an incidence in North America from 1 to 2 cases per 100,000 population.

Incidence may significantly differ geographically, as in regions of East Asia, East Europe, and South America. Residents of the Indo-Gangetic belt, particularly females of northern India (21.5/100000) and south Karachi Pakistan (13.8/100000), have been reported as one of the highly affected population in the world. In southern Chile, the rate of GBC reaches 12.3/100000 for males and 27.3/100000 for females [1].

GBC is often found incidentally after an elective or emergent laparoscopic cholecystectomy for gallstone disease or cholecystitis. The main risk factors associated with the development of cancer include the following:

- Female:male ratio (1.3–3.5:1) [2]
- History of gallstones/cholecystitis [3–8]
- Ethnic groups: Native American, Mexican, East Asian, Hispanic [9]
- Obesity and a high carbohydrate diet [10, 11]
- Anomalous pancreaticobiliary duct junction (APBDJ) [12, 13]
- Chronic GB infection (*S. typhi*) [14]
- Age (increased incidence) [15]
- Previous gastric surgery [16]

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Definitions/Terminology

- *Simple cholecystectomy (SC)*: removal of the gall bladder and a portion of the cystic duct performed laparoscopically or open. Simple cholecystectomy is conducted in a subserosal plane.
- *Radical cholecystectomy (RC)*: removal of the gallbladder including a subsegmental or segmental 4B/5 liver resection, removal of the portal/hepatoduodenal lymph nodes and possible common bile duct excision (depending upon cystic duct margin status) with appropriate reconstruction.

Incidental Gallbladder Cancer (IGBC)

Almost 50% of all patients who present with gallbladder cancer are detected incidentally during or after elective/emergent cholecystectomy. Cancers detected at the time of surgery are referred to as incidental gallbladder cancer (IGBC). In most cases, cancer is diagnosed by a pathologist after the initial cholecystectomy (index cholecystectomy, IC). Following this IC, patients undergo clinical staging to complete later an oncologic extended resection and ensure removal of any local residual cancer.

There is conflicting data whether non-oncologic index cholecystectomy leading to discovery of IGBC negatively impacts survival. Early studies showed that long-term survival was not worse for patients with IGBC who undergo oncologic extended resection after prior simple cholecystectomy than for patients with non-IGBC who undergo upfront radical cholecystectomy [17–19].

However, recent data suggests that tumor disruption, such as in patients with the tumor in the dissection plane of a routine cholecystectomy (T2b, hepatic- side tumors), has a negative survival impact from IC [20]. Therefore, in trying to favor a single-time oncologic operation, a high level of suspicion should be kept before index cholecystectomy in patients with thickened gallbladder/chronic inflammatory changes in the preoperative imaging. Surgeons may change their approach (laparoscopic to open) if there is a high preoperative level of suspicion and be prepared for frozen section to decide upon completion of radical surgery favoring a single-time operation.

Staging

Unfortunately, less than 25% of patients will present with disease amenable for curative intent surgery at the time of diagnosis [21–24]. The high incidence of patients presenting with advanced disease, spillage of bile and tumor cells during initial cholecystectomy, evidence of rapid progression, and dismal prognosis when important residual disease is left after the first operation highlight the role of accurate restaging before oncologic extended resection.

The role of routine staging laparoscopy and paraaortic lymph node biopsy is a matter of debate to prevent a futile radical (most commonly open) surgery.

CT and MRI

- CT and MRI are the most common imaging techniques used to evaluate local and distant extension of disease and recognize the relationship between localized or residual tumor and nearby vascular structures and the biliary tree.
- MRI has a higher yield in detecting smaller liver metastatic lesions and their relationship with intrahepatic ducts. However, it has well-recognized limitations for the detection of tumor recurrence mostly related to difficulty in differentiating residual/recurrent tumor from surgically induced scarring or inflammatory changes.

PET-CT

- Limitations of cross-sectional imaging studies to restage patients with residual disease have prompted exploration of the added diagnostic value of FDG PET-CT. Functional imaging prior to attempted curative intervention could improve the pre-treatment selection of patients who might potentially benefit from such interventions.
- FDG PET-CT has been reported to improve the sensitivity to detect non-clinically evident metastatic disease. FDG PET-CT may change management by identifying metastatic disease not seen in previous studies in 23–25% of cases [25, 26].
- However, other studies have proven that sensitivity and positive predictive values of FDG PET-CT for residual disease may be as low as 28.5% and 20%, respectively, particularly among those patients with small volume carcinomatosis and signet ring cell tumors [25].
- These studies showed that the use of PET is definitively helpful in 5% and confirmatory in 15% of cases. However, in 3% of patients it may underestimate signs of unresectable disease. In the majority of patients, CT and PET were completely concordant and PET did not add any information [27].
- With modern high-quality cross-sectional imaging, it is uncommon for PET findings to be the sole determinant of resectability [27]. FDG PET-CT is therefore not routinely recommended unless there is persistent imaging uncertainty.

Staging Laparoscopy

- Staging laparoscopy identifies metastatic disease/locally advanced deemed unresectable in 27.6% of patients with suspected GBC [28].
- The yield of staging laparoscopy for identifying metastatic disease is higher among poorly differentiated, T3 or positive-margin gallbladder tumors [29].

Routine Paraaortic (Station 16b1) Lymph Node Biopsy.

- Involvement of paraaortic (16b1) lymph node in GBC is a sign of advanced disease with a prognosis equivalent to that of distant metastases [30].
- The appearance (size >10 mm and heterogeneous internal architecture) of the 16b1 lymph nodes on CT of the abdomen has been reported to be useful in predicting metastatic involvement in some studies; however, others have not found these factors to be good predictors of metastatic disease [31, 32].
- Routine 16b1 LN biopsy has proven to prevent non-therapeutic radical resection in 18.6% of patients deemed resectable on preoperative staging [33].

AJCC Eighth Edition

The recommended staging system is the International Union Against Cancer and American Joint Committee on Cancer (UICC/AJCC), eighth edition, with some changes introduced to the previous edition [34] (Tables 10.1, 10.2, 10.3, 10.4, 10.5).

The main change of this classification was the novel definition of T2a and T2b which effectively stratified the prognosis of patients with T2 GBC. Furthermore,

Table 10.1 Primary tumor (T)

T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1a T1b	Tumor invades lamina propria Tumor invades the muscular layer
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 serosa (visceral peritoneum) and/or directly invades the liver and/or other adjacent organ or structure, such as stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile duct
T4	Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

Table 10.2 Regional lymph node (N)

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases to 1–3 regional lymph nodes
N2	Metastases ≥4 regional lymph nodes

Table 10.3 Distant metastasis (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

Table 10.4 AJCC prognostic stage groups

T	N	M	Stage
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

Table 10.5 Survival by AJCC stage group

Presentation (AJCC staging system)	Prognosis (5-year overall survival (OS))
Early (stage 0–1)	50–100%
Advanced/regional (stage 2A-4A)	4–30%
Metastatic (stage 4B)	2%

patients with stage IIa tumors also obtained significantly improved overall survival time compared with patients with stage IIb tumors (Table 10.1). Additionally, the new N category stratified the survival of patients effectively based on the number of positive lymph nodes and not on their anatomical distribution (Table 10.2).

Management

Special Notes: (See Tables 10.6, 10.7, 10.8)

- In Ontario, all patients with known or suspected GBC should be referred for management at a high-volume hepatopancreatobiliary surgical oncology center.
- Bile spillage is estimated to occur in up to 20–40% of elective laparoscopic cholecystectomy [37–39]. Bile spillage that has occurred during laparoscopic cholecystectomy in the setting of a high-grade tumor should not delay or act as a deterrent for definitive surgery. Patients should be evaluated and treated according to the pathology of the tumor, and fitness of the patient for surgery, although they are likely at higher risk of recurrence.
- Further resection for T1b cancers has not been shown to improve overall survival but may decrease rate of recurrence [40, 41]. In reasonable operative candidates, recommendation is to proceed with segment 4B/5 resection and lymphadenectomy (Table 10.6).

Table 10.6 General approach

Gallbladder Polyps/ adenoma	Incidental finding Intraoperative diagnosis/ pathologic diagnosis	Suspected resectable GBC	Unresectable GBC
History and physical exam Ultrasound imaging Diagnostic workup should proceed as for suspected GBC if suggested by abnormal features on initial imaging For polyps of a size ≥1 cm, surgery is advised Consider laparoscopic cholecystectomy including cystic duct LN for 1–2 cm polyps, and if the polyp position is favorable (on the contralateral wall to the bare area of the liver) All specimens should be removed in a bag including cystic lymph node Gallbladder perforation and bile spillage should be avoided Open cholecystectomy for larger polyps [35, 36] where preoperative imaging or intraoperative frozen section will dictate whether adjacent liver is removed en bloc	0.3–2% of laparoscopic cholecystectomies Intraoperative finding [2]: Intraoperative staging Frozen section of gallbladder sent after extraction of entire specimen in a bag Remove cystic lymph node Alert the pathologist as the specimen will be processed differently Evaluate for definitive surgery, depending on surgeon experience and tumor resectability If in doubt, close and refer to HPB Cancer Centre Postoperative finding: History and physical exam Pathology/operative note review If T in situ or T1a No further evaluation needed, clinical surveillance only. No consensus on imaging follow-up If T1b or higher Labs – Liver function, Ca 19–9, CEA Imaging – CT chest, abdomen, pelvis; MRI Radical cholecystectomy	History and physical exam Labs: Including liver function tests, Ca 19–9, CEA Imaging: CT chest and triphasic liver MRI/MRCP liver Consider staging laparoscopy (if ≥T2, equivocal imaging) Avoid biopsy if lesion is deemed surgically resectable ⇒ Jaundice is frequently a dismal prognostic indicator, and many would preclude surgery ⇒ Consider ERCP if drainage required, although percutaneous approach usually allows better access to proximal hepatic ducts	History and physical exam Labs: Including liver function tests, Ca 19–9, CEA Imaging: CT chest, abdomen, pelvis MRI/MRCP Consider biopsy of distant disease (percutaneous) Decompression if jaundice present (PTC with internalization if central obstruction, ERCP if distal obstruction) Medical/ radiation oncology referral

GBC gallbladder cancer, *ERCP* endoscopic retrograde cholangiopancreatography, *EUS* endoscopic ultrasound, *PTC* percutaneous transhepatic cholangiography/catheter

- A negative frozen section of the cystic duct margin is mandatory during all radical cholecystectomies if the extrahepatic bile duct is not being resected.
- Jaundice is a poor prognostic marker (median disease-specific survival was 6 months vs 16 months in non-jaundiced patients; no jaundiced patients were alive at 3 years). Surgery exploration may not be warranted in this patient population [42].
- The presence of residual cancer after incidental cholecystectomy (pT2b or higher, positive cystic duct margin or pN+) is associated with poor disease-

Table 10.7 Management of advanced GB tumors

Clinical scenario	Surgical management
T2: Penetrates perimuscular connective tissue, no extension beyond serosa or into liver *T2a*: Peritoneal side, without involvement of the serosa *T2b*: Hepatic side, with no extension into the liver *T3: perforates serosa and/or directly invades the liver or other adjacent structure*	T2: LN metastases 20–62% (portal node involvement), 20% celiac and peripancreatic nodes [50] Segment 4b/5 non-anatomic liver resection, with a 2 cm clear margin, recommended for T2 and T3 lesions LN harvest recommended to include porta hepatis, gastrohepatic ligament, retroduodenal nodes
T4: invades main portal vein/hepatic artery or invades two or more extra hepatic structures	Radical hepatectomy (extended right hepatectomy or right trisectionectomy) +/− PVR in very selected cases (see note) LN harvest recommended to include porta hepatic, gastrohepatic ligament, retroduodenal nodes

LN lymph nodes, *PVR* portal vein resection

Table 10.8 Unresectable/metastatic disease

Criteria of unresectability	Surgical management
Metastatic disease: To liver, lung, peritoneum, distant lymph nodes (celiac, SMA nodes) Patient factors: Comorbidities rendering patient unable to tolerate potentially curative surgery Anatomical factors: There is no consensus for local extension of tumor that precludes resection. Tumor encasement of bilateral hepatic arteries or the common hepatic artery, however, is a contraindication to surgery	Consider non-operative approach to palliation if able (e.g., endoscopic stent/PTC placement) [59]

SMA superior mesenteric artery, *PTC* percutaneous transhepatic cholangiography/catheter

specific survival even when R0 resection is achieved after oncologic extended resection. Median disease-free survival (DFS) is 11.2 vs. 93.4 months, ($p < 0.0001$) and disease-specific survival (DSS) 25.2 months vs. not reached, ($p < 0.0001$), when compared to no-residual cancer after IC [43–45].

- Extended lymphadenectomy is required for IGBC, independent of cystic duct lymph node status. Cystic duct node positivity has been associated with positive perihilar nodes (odds ratio 5.2, $p = 0.012$), but not with common hepatic artery, pancreaticoduodenal nor paraaortic lymph nodes, which have an OS comparable to M1 disease [46].
- Port/Trocar site metastases, the implantation of disease at any of the port sites (not limited to the extraction site), was originally estimated to occur in 10–18% cases after laparoscopic cholecystectomy [47]. More recent data suggests, however, that the incidence of abdominal wall recurrence after laparoscopic procedure is low (7%) and comparable to open technique (5.1%) [48].

Port-site excision during re-resection for IGBC has been proven in more recent data not to be associated with improved overall survival and has the same distant disease recurrence compared to no port-site excision; therefore, it is no longer recommended routinely [49].

- Patients without residual cancer at oncologic extended resection and positive incidental cystic duct node may have similar DSS to patients with negative nodes, 70 vs 60% ($p = 0.337$) [46].
- *Quality Indicators*:
  - *Pathologic review* should include location and size of tumor, depth of invasion, presence of perineural/vascular/lymphatic invasion, cystic duct node involvement, surgical margin status (particularly cystic duct margin), and evidence of perforation of gall bladder.
  - *Operative note* should include whether gallbladder was removed intact, evidence of perforation or spillage of bile, excision of cystic node, removal of gallbladder using a bag with identification of the port site used, and use of wound protector.

Special Notes:

- Early re-exploration for patients with incidentally found T2 lesions [51] (Table 10.7).
- Adequacy of tumor resection (R0 status), rather than the extent of resection, predicts survival. Therefore, surgical resection should be tailored to obtaining complete oncologic clearance of the tumor and adequate lymphadenectomy [52].
- Extent of surgery for formal resection is determined by the location and stage of the tumor, as well as the intrahepatic anatomy and cystic duct margin.
- Right trisectionectomy is necessary for cancers involving the right hepatic artery and advanced lesions. PVE may be useful in these cases (Table 10.7).
- Pancreaticoduodenectomy has been reported for distal lesions, although 5-year survival is reported at 9–10% in two small series and median survival of 21 months (one alive at 42 months) in another [53–55] series. The main limitation of a local (segment 4b/5) resection is the distance between the GB and the segment 8 portal pedicle, which can be as little as 2 mm away. Limited 4b/5 resections should only be considered in T2 lesions located in the fundus where an adequate (2 cm) margin can be obtained by ligation of the segment 5 portal pedicle with preservation of the segment 8 portal branches.
- Routine bile duct resection does not improve overall survival [56, 57]. Resection of the extrahepatic biliary duct (EHBD), however, is indicated in cases where the cystic duct margin is positive for cancer or high-grade dysplasia [58].
- Extrahepatic bile duct resection may be indicated in cases of cystic duct and Hartman's pouch cancers, as well as cases where resection of the EHBD is required to achieve adequate oncologic clearance due to proximity of GB or tumor infiltration of the EHBD.
- The presence of metastatic disease during exploration is considered unresectable (Table 10.8).

Landmark Publications

Prospective randomized control trials (RCTs) regarding surgical management of this disease are few due to the relative rarity of the disease. Surgical management is largely dictated by consensus statements formed by high-volume centers. Most data have been developed from retrospective series with limited number of patients. Any reference to staging refers to the eighth edition of UICC staging (Table 10.9).

Table 10.9 Restropective reviews and RCTs in GBC

Topic	Study	Methods	Results
Stage 1	Wagholikar et al., 2002 [60]	Retrospective review *n* = 14 patients Early stage 12 patients treated with SC 2 patients treated with RC	Median survival (*n* = 14): 42 months 5-yr survival (*n* = 14): 68% LR in 5/12 patients: All had pT1b cancer treated with SC pT1a lesions can be treated with SC Recommend T1b be treated with RC
	Wakai et al., 2001 [61]	Retrospective review *n* = 25 patients Patients with T1b cancer 13 patients treated with SC 12 patients treated with RC	10-yr survival (*n* = 25): 87% No difference in survival in patients with SC (100%) vs. RC (87%) No LR in either group pT1b lesions can be treated with SC without impact on survival
Stage 2	Taner et al., 2008 [62]	Retrospective review *n* = 131 patients 45 patients treated with SC 60 patients treated with RC 25% patients had T2	Median survival(*n* = 131): 11 months RC associated with longer survival than SC (HR 0.42) for pT2 or higher RC for patients with pT2 tumors or greater (achieves longer term survival, whether administered as the initial surgery or after incidental discovery)

(continued)

Table 10.9 (continued)

Topic	Study	Methods	Results
Stage 3/stage 4A	Sasaki et al., 2006 [63]	Retrospective review *n* = 65 patients Advanced GBC 27 patients with N1 disease 6 underwent PD with hepatectomy	Overall 5-yr survival, N1 disease (*n* = 21): 46.8% 16 patients recurred after curative OR (lymph node and distant metastases) Surgical resection recommended only if R0 margin possible High morbidity and mortality rates associated with extensive surgery, to be avoided in patients with para-aortic nodal disease
Medical oncology	UK-ABC-02 Valle et al., 2010 [64]	RCT phase 3, conducted in 37 centers in the UK *n* = 410 patients Unresectable, recurrent, or metastatic biliary cancer (included intra−/extrahepatic cholangiocarcinoma, ampullary, gallbladder cancer) Gemcitabine + cisplatin vs. gemcitabine alone for 24 weeks	Median survival was 11.7 vs. 8.1 mos for the Gem-Cis vs Gem-alone groups, respectively (HR 0.64) Significant improvement in progression-free survival, 8 mos vs. 5 mos Gem-Cis vs. Gem groups, respectively (HR 0.63) The combination of Gem-Cis chemotherapy for advanced/metastatic disease gave an average of 3.6 mos longer life than gemcitabine alone, with limited toxicity, and represented an appropriate option for treatment in these patients

Table 10.9 (continued)

Topic	Study	Methods	Results
	BILCAP Primrose et al., 2019 [65]	RCT phase 3, conducted in 44 centers in the UK *n* = 447 patients Histologically confirmed cholangiocarcinoma or muscle-invasive gallbladder cancer who had undergone a macroscopically complete resection with curative intent Patients were randomly assigned 1:1 to receive oral capecitabine or observation commencing within 16 weeks of surgery	The prespecified per-protocol analysis (210 patients in the capecitabine group and 220 in the observation group): Median overall survival was 53 months (95% CI: 40 to not reached) in the capecitabine group and 36 months (30–44) in the observation group (adjusted HR 0·75, 95% CI 0·58–0·97; *p* = 0·028) Median recurrence-free survival was 25·9 months (95% CI 19·8–46·3) in the capecitabine group and 17.4 months (12.0–23.7) in the observation group
Radiation oncology	Kresl et al., 2002 [66]	Retrospective review *n* = 21 patients (stage III-IV) Adjuvant CRT (5-FU + EBRT 54Gy)	5-yr OS = 33% (21 patients), 64% if R0 resection with the addition of radiation When compared to historical surgical control group, improved 5-yr OS with R0 resection and addition of radiation (33% vs. 64%)

OS overall survival, *SC* simple cholecystectomy, *RC* radical cholecystectomy, *GBC* gallbladder cancer, *LR* locoregional recurrence, *PD* pancreaticoduodenectomy, *R0*: negative microscopic margins, *CRT* chemoradiotherapy, *EBRT* external beam radiotherapy

Referring to Medical Oncology

1. All patients who are stage 2 or higher for adjuvant chemotherapy [65].
2. All metastatic patients considered for palliative therapy.

Referring to Radiation Oncology

1. All patients who are T2 or higher and considered for adjuvant therapy (though there is limited evidence for this). Adjuvant treatment can be considered for R1 resection.
2. Palliative patients for consideration of symptomatic control.

Referring to MCC

1. All patients with T1b disease or higher.

Toronto Pearls

- All incidental T1b and higher cancers should be considered for re-resection. Aggressive surgery in early-stage disease is associated with potential for cure.
- Laparoscopic radical cholecystectomy has been reported with reasonable oncologic outcomes, but the data is not robust enough for it to be routinely recommended [67, 68].
- Formal resection should be tailored to achieve complete oncologic (R0) clearance of the tumor.
- Limited resection (seg4b/5) should be used selectively in T1b/T2 and T3 tumors located in the fundus where adequate tumor clearance can be achieved at the bifurcation of the right portal structures.
- Bile duct resection may be performed selectively based on cystic duct margin or oncologic clearance of the tumor.
- Portal lymphadenectomy should be performed for all cases with T1b and higher tumors.
- Adjuvant therapy should be considered for stage 2 disease and higher.

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