

ORIGINAL ARTICLE

Gallbladder Cancer: expert consensus statement

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Abstract

An American Hepato-Pancreato-Biliary Association (AHPBA)-sponsored consensus meeting of expert panellists was convened on 15 January 2014 to review current evidence on the management of gallbladder carcinoma in order to establish practice guidelines. In summary, within high incidence areas, the assessment of routine gallbladder specimens should include the microscopic evaluation of a minimum of three sections and the cystic duct margin; specimens with dysplasia or proven cancer should be extensively sampled. Provided the patient is medically fit for surgery, data support the resection of all gallbladder polyps of >1.0 cm in diameter and those with imaging evidence of vascular stalks. The minimum staging evaluation of patients with suspected or proven gallbladder cancer includes contrasted cross-sectional imaging and diagnostic laparoscopy. Adequate lymphadenectomy includes assessment of any suspicious regional nodes, evaluation of the aortocaval nodal basin, and a goal recovery of at least six nodes. Patients with confirmed metastases to N2 nodal stations do not benefit from radical resection and should receive systemic and/or palliative treatments. Primary resection of patients with early T-stage (T1b–2) disease should include en bloc resection of adjacent liver parenchyma. Patients with T1b, T2 or T3 disease that is incidentally identified in a cholecystectomy specimen should undergo re-resection unless this is contraindicated by advanced disease or poor performance status. Re-resection should include complete portal lymphadenectomy and bile duct resection only when needed to achieve a negative margin (R0) resection. Patients with preoperatively staged T3 or T4 N1 disease should be considered for clinical trials of neoadjuvant chemotherapy. Following R0 resection of T2–4 disease in N1 gallbladder cancer, patients should be considered for adjuvant systemic chemotherapy and/or chemoradiotherapy.

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Pathologic evaluation of routine cholecystectomy specimens and gallbladders with neoplastic changes and polyps

Gallbladder carcinoma (GBC) is a rare malignancy, but in selected areas of high incidence, such as India, Chile and Japan, it is a significant source of mortality.^{1,2} Because of its

low incidence in most Western countries, GBC has been understudied, leading to variation in approaches to the initial pathologic evaluation, classification and staging of the disease.³

Protocol for routine pathologic assessment of gallbladder specimens

Historically, pathologic under-sampling of gallbladder specimens has led to under-diagnosis and under-staging. For those patients in whom there is no clinical or imaging suspicion for GBC and no apparent abnormality on gross examination,

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there is no consensus on a uniform pathologic examination protocol. In many countries no microscopic examination is recommended or performed in these situations.⁴ Given that most cases of GBC are clinically unapparent on gross evaluation, this implies that GBC may go undiagnosed in several thousand cholecystectomies per year.⁵

To address this issue, a specific stepwise pathology sampling protocol has been proposed.^{5,6} Particularly in areas of high GBC prevalence, in gallbladders that appear normal on gross examination, a minimum of three random areas and the cystic duct margin should be submitted for microscopic assessment. A finding of dysplasia or neoplasia on initial random sampling prompts a complete sampling of the gallbladder. By contrast with some reports,⁴ this practice is supported by data that indicate that a significant number of patients initially found to have dysplasia will harbour an invasive malignancy.⁶

High-risk features indicate the need for more extensive routine sampling of the gallbladder

It has been established that certain disorders are associated with GBC, including choledochal cysts, an anomalous union of the pancreaticobiliary ducts and primary sclerosing cholangitis.¹ In such cases, a more thorough examination of the gallbladder is warranted. More importantly, in cases with hyalinizing cholecystitis, characterized by minimal to no calcifications ('incomplete porcelain gallbladder'), the incidence of subtle invasive carcinoma appears to be very high and therefore these cases ought to be thoroughly examined.⁷

Pathologic assessment of mass lesions of the gallbladder

In gallbladder specimens with mass lesions suspicious for or proven to be GBC, a complete analysis of the specimen is indicated.^{5,6} Particularly in high-risk regions with frequent cases of localized GBC, it is prognostically important to distinguish *early* (muscle-confined) from *advanced* (through the tunica muscularis) GBC.⁶ Data on longterm outcomes indicate that when extensive and careful sampling confirms the absence of advanced carcinoma, patients with early-stage GBC have a very good prognosis (10-year survival of 90%).^{8–10} Additional pathologic prognostic factors that should be reported in cases of confirmed GBC include involvement of Rokitsky–Aschoff sinuses, multifocality of dysplasia, and involvement of the hepatic versus free peritoneal surface of the gallbladder.^{8,9} The determination of cystic duct margin involvement is potentially important in subsequent surgical decision making. Thus, adequate sampling to identify these prognostic findings is crucial for proper staging and management protocols.

Pathologic evaluation of gallbladder polyps

Most polypoid masses of the gallbladder are small cholesterol or fibromyoglandular lesions with no malignant potential.¹¹ True papillary neoplasms (formerly referred to as adenomas)

do harbour a malignant potential, thought to be proportionate to their overall size and degree of vascularity. In fact, gallbladder polyps of <1.0 cm in diameter seldom prove to be neoplastic. By contrast, pathologic analyses suggest that most polyps of >2.0 cm contain neoplasia. Although criteria for the threshold polyp size that should indicate cholecystectomy are subject to debate,¹² there appears to be an increased incidence of malignancy in polyps of >1.0 cm in diameter and in those with a vascular pedicle,^{13–18} both of which are most commonly determined with preoperative transcutaneous ultrasound examination with Doppler flow studies.

Classification of papillary gallbladder neoplasms

In a recent effort to align with the classification of papillary tumours of the pancreaticobiliary tree, the category of intra-cholecystic papillary tubular neoplasm (ICPTN) was created as an umbrella term for all pre-invasive adenomatous polypoid and papillary neoplasms of the gallbladder of >1.0 cm in diameter.¹¹ Regardless of the names assigned to these lesions, all of these polypoid papillary lesions should be submitted for microscopic examination. In cases of high-grade dysplasia in the polyp, extensive sampling of the remaining gallbladder is warranted because carcinomatous changes frequently occur in the seemingly uninvolved portions.¹¹

In summary, the systematic evaluation of all gallbladder specimens in pathology laboratories is crucial for the accurate diagnosis and staging of gallbladder neoplasms. For gallbladders with dysplasia on initial evaluation and/or abnormalities on gross examination, including hyalinizing cholecystitis and suspicious gallbladder wall masses, extensive pathologic sampling of the specimen is warranted. In preoperatively identified polypoid lesions, a diameter of >1 cm and/or vascularity of the stalk of the polyp represent indications for cholecystectomy. Neoplastic polypoid/papillary lesions, proposed to be designated as ICPTNs, are highly analogous to their counterparts in the pancreas [intraductal papillary mucinous neoplasms (IPMNs)] or bile ducts [intraductal papillary neoplasms of the bile duct (IPNBs)], are frequently associated with more widespread atypia, and should prompt the complete examination of the remainder of the gallbladder.

Consensus statements

- Particularly in areas of high incidence, routine gallbladder specimens should be pathologically assessed and the minimum examination should include the microscopic evaluation of three sections and the cystic duct margin.
- During the initial analysis, a finding of high-grade dysplasia, hyalinizing cholecystitis and/or neoplastic polyps should prompt the complete sampling of the entire gallbladder specimen to accurately stage any associated invasive malignancy.
- Gallbladder specimens with proven cancer should be extensively sampled and prognostic factors determined, including microscopic depth of tumour invasion, tumour involvement

of the cystic duct margin, involvement of Rokitansky–Aschoff sinuses, and serosal versus hepatic surface involvement.

- Provided the patient is medically fit for surgery, data support the resection of all gallbladder polyps of >1.0 cm in diameter and those with imaging evidence of vascular stalks.

Evaluation and management of a gallbladder mass

Gallbladder cancer is an aggressive malignancy with poor prognosis. Only 25% of patients will undergo potentially curative surgery, and just 16% will survive for more than 5 years. Surgical treatment has proven to be curative in some patients, but postoperative survival is so closely associated with pathologic tumour stage that resectional surgery has as much of a role as a staging modality as it does as a therapeutic endeavour.

Because GBC is relatively uncommon, multiple longitudinal studies have included GBC along with other bile duct malignancies, such as cholangiocarcinoma. However, current evidence shows that surgical approaches, margin-free resection rates and longterm survival differ completely between these types of tumour. Therefore, GBC must be considered and treated as a separate entity.

This section focuses on current controversies in the management of the specific group of patients who present with preoperative suspicion for or a confirmed diagnosis of GBC and an intact gallbladder.

Accurate staging to predict technical and oncologic resectability

Patients who present with symptoms of indigestion, pain, weight loss and/or jaundice may be discovered to have a gallbladder mass via ultrasound study or cross-sectional imaging. Alternatively, gallbladder pathology may be incidentally identified during the work-up of other symptoms. Once identified, gallbladder masses are best evaluated by contrast-enhanced abdominal computed tomography (CT) because the additional capacity of this modality to interrogate portal nodes, peritoneal implants and vascular invasion makes it the most accurate modality with which to determine resectability.¹⁹ The diagnostic and staging accuracy of CT may be augmented by gadolinium-enhanced magnetic resonance imaging (MRI), which can provide more detailed evaluation of the common hepatic duct (CHD) /common bile duct (CBD) and liver parenchyma, especially in patients with concomitant liver steatosis or cirrhosis. The presence of lymph node (LN) metastases in GBC is often difficult to determine preoperatively; abdominal CT and MRI are reported to facilitate a detection rate of 24%.²⁰ If imaging identifies suspicious intrahepatic masses, regional lymphadenopathy and/or peritoneal implants, endoscopic, percutaneous or laparoscopic biopsy should be performed prior to resection.

In patients with known or suspected GBC, 18-FDG positron emission tomography (PET)-CT has demonstrated the ability to detect occult peritoneal, omental and/or LN metastases with sensitivity of 56%.²¹ This may be relevant in patients in whom GBC is discovered incidentally because the detection of clinically occult metastasis may help identify those patients who would not benefit from a radical resection prior to laparotomy.²²

Influence of jaundice on surgical decision making

The majority of GBC patients who present with jaundice will have disseminated disease even if it is not detectable on preoperative work-up or operative exploration. The en bloc resection of the CHD/CBD, which is frequently required in these patients, is difficult and associated with positive (R1) margin status in 40% of patients.^{23,24} Despite anecdotal reports of longer postoperative survival in GBC patients presenting with the rare combination of jaundice without nodal involvement,²⁵ even in patients with a negative (R0) margin, the median length of disease-free survival in preoperatively jaundiced patients is only 6 months.²⁶ Based on these data, preoperative jaundice should be considered a relative contraindication to radical resection of GBC.

Surgical management of the gallbladder mass

Following adequate staging to rule out distant metastases, unresectable regional nodal disease, and/or local advancement to critical hepatic vascular/biliary structures, medically fit patients should be considered for surgical exploration. The intraoperative decision making involves several key elements.

Patients without a tissue diagnosis

In many instances, there is suspicion of GBC but no tissue diagnosis prior to exploration. Although preoperative imaging can help to differentiate GBC from other benign aetiologies, such as acute and/or chronic cholecystitis, mass-forming xanthogranulomatous cholecystitis is known to masquerade as GBC.²⁷ In the absence of a preoperative diagnosis, extensive intraoperative core needle biopsy with immediate frozen-section analysis is recommended prior to committing to radical resection. In the frequent presentation of xanthogranulomatous cholecystitis associated with large gallstones and extensive inflammation that limits the ability to perform simple cholecystectomy, cholecystotomy with stone removal is recommended only after intraoperative biopsies have proved negative for malignancy.^{27,28}

Role of staging laparoscopy

Given the propensity of GBC to involve regional nodes and peritoneal surfaces,²⁹ staging laparoscopy can help to prevent unnecessary surgical exploration in 38–62% of patients.³⁰ Up to 23% of cases can be determined to be oncologically unresectable with simple laparoscopy. The addition of laparoscopic

ultrasound and intraaortocaval LN frozen-section evaluation can potentially further increase the detection rate in patients who will not benefit from radical resection.³¹ Based on the high incidence of positive findings, staging laparoscopy is recommended prior to laparotomy for all instances of suspected or proven GBC.

Intraoperative LN evaluation

Gallbladder cancer most commonly spreads from the gallbladder to the periportal LNs and then to the aortocaval station, but may also cross to the coeliac nodal station before advancing to more distant axial sites. Longterm survival has been reported in patients with involvement of the pancreaticoduodenal and hepatic artery LNs (N1). By contrast, no survival benefit is evident in those with involved para-aortic, coeliac or superior mesenteric artery (SMA) nodes (N2).^{32,33}

Data from high-volume centres demonstrating that up to 26% of GBC patients will have axial LN involvement (aortocaval/coeliac) that would negate any benefit of radical surgery indicate that aortocaval LN sampling should be performed routinely at the initiation of the operation.^{32,33} Although periportal regional LN (N1) involvement does not contraindicate radical resection, it is a very poor prognostic indicator, and therefore the presence of an institutional neoadjuvant therapy protocol for locally advanced GBC may indicate that pathologic confirmation of regional disease should discontinue the immediate plan for up-front resection in favour of the prospective evaluation of pre-resection chemotherapy and/or chemoradiotherapies.³⁴

Laparoscopic and open approaches to definitive resection

Minimally invasive resection of intact GBC has been performed at specialized expert centres. These centres have reported safety and feasibility outcome data for T1b, T2 and even T3 tumours that rival the outcomes of open surgery,³⁵ but no randomized studies have objectively compared the minimally invasive and open surgery approaches. Oncologic adequacy data on LN sampling and surgical/hepatic parenchymal margins are preliminary and incomplete. Given the current data, minimally invasive surgery in oncologic GBC resection is not the standard of care and its use should be limited to specialized centres that have demonstrated the ability to overcome the technical challenges associated with: (i) adequate portal and aortocaval LN sampling; (ii) R0 liver transection margins, and (iii) CHD/CBD resection or reconstruction.³⁵

Extent of primary resection

After evaluation for peritoneal and regional nodal disease, patients with tumours limited to the wall of the gallbladder (T1b–2) are recommended to undergo radical cholecystectomy with en bloc resection of adjacent liver parenchyma. In these

instances, CHD/CBD resection can be reserved for gross involvement by direct contact or microscopic involvement of the intraoperatively evaluated cystic duct margin.²⁴ Regardless of final margin status, bile duct involvement by GBC portends a poor prognosis, probably because it is frequently associated with regional lymphatic invasion.²³

Management of locally advanced GBC with adjacent organ involvement

For T3 or T4 tumours, the extent of the primary resection is debatable. As direct invasion of adjacent organs that normally contact the gallbladder (duodenum or colon) does not necessarily indicate nodal involvement and is denoted as T3 in the staging system, en bloc adjacent organ resection is permissible but has not been associated with improved long-term survival.²⁴ Likewise, longterm survival after radical resections that included major hepatectomy, CHD/CBD and/or vascular resection or reconstruction has been anecdotally reported,^{24,36} but these radical resections have not been associated with longer disease-free or overall survival on a population basis. Instead, they are associated with increased morbidity and mortality. Radical resections of locally advanced primary tumours should, therefore, be performed only in medically fit patients after multidisciplinary discussion. Although R0 resection for GBC is associated with longer survival, tumour biology and stage, rather than the extent of resection, are the most important predictors of survival after surgery.^{23,37}

Extent of lymphadenectomy

Positive regional LNs are predictors of worse survival in GBC. By incorporating the biology of disease (positive LN) and the quality of lymphadenectomy (total LN count), the LN ratio has been shown to be an important predictor of survival after surgery.³⁸ Based on these data, adequate staging requires the retrieval of a minimum of six nodes.³⁹ To achieve this, dissection beyond the immediate portal nodes is frequently required.

Postoperative follow-up

Few published studies have focused on the patterns and timing of recurrence after resection of GBC, but up to 50% of resected patients fail within 2 years of surgery, typically with a combination of regional and distant recurrence.³³ As such, surveillance follow-up of asymptomatic post-resection patients who are not treated with adjuvant therapy is probably best accomplished with chest/abdomen/pelvis CT at intervals of 3–4 months.

Consensus statements

- The minimum staging evaluation of patients with suspected or proven GBC includes contrasted cross-sectional imaging and diagnostic laparoscopy.

- Adequate lymphadenectomy includes intraoperative assessment of any suspicious regional nodes, evaluation of the aortocaval nodal basin, and the recovery of at least six nodes. Patients with confirmed metastases to N2 nodal stations do not benefit from radical resection and should receive systemic and/or palliative treatments.
- Primary resection of patients with early T-stage (T1b–2) disease should include en bloc resection of adjacent liver parenchyma. Resection of the CHD/CBD is only beneficial or required in cases of gross direct extension or microscopic involvement of the cystic duct margin.
- In patients with locally advanced primary tumours, and particularly in those with jaundice, the risk : benefit ratio of radical surgery, to include major hepatectomy, vascular and/or adjacent organ resection, is marginal and these methods should only be considered in expert centres after multidisciplinary discussion.
- Minimally invasive GBC resections should be limited to early T-stage patients treated by expert surgeons who have demonstrated outcomes using this approach that are oncologically equivalent to those of open surgery.

Evaluation and management of incidentally discovered GBC

After an incidental GBC is discovered after cholecystectomy, the rationale for re-resection is based on the incidence of residual disease, the ability of additional staging information to prognosticate survival and to direct adjuvant therapy, and whether re-resection improves patient outcomes.

Incidence of residual disease

The incidence of residual disease varies by the T-stage classification of the primary tumour. The incidence of finding residual disease at any site can be as high as 37.5% in T1 tumours, 56.7% in T2 tumours, and 77.3% in T3 tumours.⁴⁰ Incidences of residual disease in the liver bed and/or LNs are lower, ranging from 12% in patients with T1 tumours to 46% in those with T3 tumours.⁴⁰ A collaborative group study involving 21 European centres reported the incidence of residual disease to be as high as 82% in patients with T2–3 tumours,⁴¹ and an experience from Chile yielded a similar rate of 72% for the finding of residual disease at re-exploration.⁴²

Re-resection and survival outcomes

In the absence of prospective clinical trials, observational studies indicate that complete resection of residual disease is associated with improved survival. The European collaboration (French Association of Surgery – Gallbladder Cancer) [AFC–GBC] reported a 5-year survival rate of 41% in patients who underwent re-resection compared with only 15% in those who did not.⁴¹ The survival advantage of a complete R0 resection,

independent of the presence of residual disease at re-exploration, has also been demonstrated.⁴² More recently, the University of Toronto reported improved survival in patients in whom curative resection was performed, thus supporting re-resection.⁴³ When assessed separately by T-stage classification, re-resection has been associated with improved survival in both T2 and T3 tumours.^{41,44}

Whereas most authors agree that T1a tumours are adequately treated with cholecystectomy alone, re-resection of T1b tumours is more controversial. A decision-analytic Markov model performed specifically for T1b tumours suggests that re-resection is associated with improved 5-year survival (87.5% versus 61.3%), and that the number of years gained was greatest in younger patients, regardless of gender.⁴⁵ A recent study using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database demonstrated a similar finding in that radical resection was associated with improved survival in patients with T1b tumours but not in those with T1a tumours.⁴⁶ Thus, re-resection is indicated for T1b, T2 and T3 incidentally discovered GBCs.

Preoperative evaluation: the role of PET

Although it is standard practice to obtain high-quality cross-sectional imaging in the form of CT or MRI, the utility of PET in this setting is unknown. A group from the Memorial Sloan–Kettering Cancer Center (MSKCC) reported that, when assessing patients with incidental GBC, PET scans altered management in only 13% of patients.⁴⁷ Although Shukla *et al.* reported on their experience using PET prior to re-resection, it is not clear how frequently PET detected disease that was missed on multi-detector CT in M1 patients.⁴⁸ Furthermore, analysis that determined that PET can correctly identify 33% of patients to have inoperable disease that was missed on CT was conducted in only three patients.⁴⁸ A group from Chile reported that PET-CT altered management in 38% of patients; however, patients did not undergo CT or MRI alone and hence it was not possible to surmise the unique contribution of PET to the improved detection of disease.²² Thus, the role of PET prior to re-resection surgery remains undetermined, but it is likely that PET should be selectively utilized only when questionable or concerning features are apparent on CT or MRI.

Operative strategy

Staging laparoscopy

Prior to performing laparotomy at the time of re-resection, a staging laparoscopy may be performed. Goere *et al.* examined the utility of this approach in a mixed cohort of patients with biliary cancer and found it to give the highest yield (37% determined to be unresectable) in patients with GBC.³⁰ However, this study did not include patients with incidentally discovered GBC, but instead referred to those in whom a gallbladder mass was apparent on preoperative imaging. Focusing

only on patients presenting with incidental GBC, the group from MSKCC found that of patients who underwent staging laparoscopy prior to laparotomy, 20% of patients with distant disease were identified with laparoscopic evaluation. Predictors of a positive laparoscopy included T3 disease, a poorly differentiated tumour and a positive margin at the time of original cholecystectomy.⁴⁹ Thus, it seems that the yield of staging laparoscopy is probably highest when the technique is performed selectively, using adverse pathologic characteristics such as T3 disease, poor differentiation and positive margin status to guide selection.

Port site resection

In an attempt to lower the rate of wound recurrence, some authors have advocated the use of port site resection at the time of re-resection in view of the possibility of tumour contamination at the time of laparoscopic cholecystectomy. However, this practice is not supported by the literature. Fuks *et al.* reported that only one of 54 patients who underwent port site resection was found to have disease, and that this patient developed and died from generalized peritoneal disease soon afterwards.⁴¹ Port site resection was not associated with improved survival and was associated with a 15% incisional hernia rate.⁴¹ Maker *et al.* reported a similar finding at MSKCC, where port site disease was associated with the development of generalized peritoneal disease and port site resection was not associated with improved survival.⁵⁰ Thus, routine port site resection is not indicated.

Lymph node dissection

The incidence of LN involvement varies by T-stage, approximating 12%, 31% and 45% in patients with T1b, T2 and T3 tumours, respectively.⁴⁰ In a 2009 SEER study, lymphadenectomy in conjunction with radical resection was associated with improved survival in comparison with radical resection alone in patients with T1b and T2 tumours.⁵¹ Others have shown that excision of at least five LNs was associated with improved survival compared with a lesser LN yield.⁵² These and other data have led to the recommendation that six LNs should be removed for accurate staging.³⁹ However, the median LN yield reported in most studies is only two or three, which indicates the need for improvement in this area. Biopsy of N2 level nodes may provide prognostic benefit and may be used to tailor surgical approaches; however, formal LN dissection should be limited to the hepatoduodenal ligament, as extended LN excision (i.e. coeliac or para-aortic) is not associated with improved outcomes because the involvement of these distant nodes represents distant metastatic disease.⁵³

Extent of liver resection

The goal of the liver resection is to obtain an R0 resection.⁴⁰ The routine performance of a major hepatectomy compared

with a partial hepatectomy (non-anatomic resection of the gallbladder bed) or a formal segment IVb/V resection has not been associated with improved survival, but has been linked to increased morbidity.²⁴ This has been demonstrated repeatedly in multiple studies^{41,42,52} and the trend over time has favoured the performance of a lesser resection, as long as negative margins are achieved.

Bile duct resection

Similarly to major hepatectomy, routine bile duct resection has been shown repeatedly to have no impact on survival, but, rather, to increase morbidity.^{24,40,44} Furthermore, bile duct resection has not been associated with a higher LN yield.⁴⁰ Thus, bile duct resection should not be routinely performed. It may be indicated by a positive cystic duct margin at cholecystectomy or when it is necessary to achieve an oncologically sound re-resection with a negative margin. Allowing sufficient time for the resolution of portal inflammation following cholecystectomy aids in the identification and preservation of biliary structures.

Consensus statements

- Patients with incidentally identified T1b, T2 or T3 disease in a cholecystectomy specimen should undergo re-resection unless this is contraindicated by advanced disease or poor performance status.
- Prior to re-resection, patients should undergo high-quality cross-sectional imaging with CT or MRI; PET should be used selectively to clarify features of concern identified on CT or MRI.
- Staging laparoscopy should be considered prior to laparotomy, particularly in patients with T3 tumours and adverse pathologic characteristics. Routine port site excision is not indicated.
- Re-resection should include portal lymphadenectomy and excision of all LNs in the hepatoduodenal ligament. Extended LN dissection is not routinely indicated.
- The goal of re-resection is an R0 resection. Major hepatectomy and/or bile duct resection is not routinely indicated unless these are required to achieve an R0 margin.

Advances in neoadjuvant and adjuvant chemotherapy and radiation approaches to GBC

Gallbladder cancer epidemiology and prognosis

Annually, GBC affects over 140 000 patients worldwide and over 100 000 will die each year from this aggressive disease.⁵⁴ Women are affected more often than men, and in the USA the Hispanic population and Alaskan natives have disproportionately high incidences of this disease.⁵⁵ Most patients are diagnosed at an advanced stage of disease, in which the 5-year survival rate is <10%. Surgical resection in early-stage disease

offers potential cure, but only a minority of patients (10%) are candidates for these procedures, which further contributes to the overall poor level of survival in this disease.⁵⁶

Role of adjuvant systemic chemotherapy after GBC resection

Because there is a paucity of Level I evidence provided by randomized Phase III clinical trials, adjuvant therapy guidelines for this disease are based on retrospective data analyses and expert opinion. A review of the SEER database indicates that adjuvant chemoradiation improved survival in patients with regionally advanced disease (with lymphatic or hepatic involvement).⁵⁷ One randomized Phase III study of adjuvant chemotherapy, conducted in Japan in GBC patients, demonstrated improved survival with adjuvant 5-fluorouracil and mitomycin.⁵⁸ A recent literature-based meta-analysis of biliary cancer patients receiving adjuvant therapy reported a non-significant improvement in survival in biliary cancer patients (including a large number of patients with GBC) treated with adjuvant therapy in comparison with those treated with surgery alone.⁵⁹ However, in a subset analysis the authors concluded that surgically resected patients with positive LNs or R1 resection margins derived the most benefit from adjuvant chemoradiation or chemotherapy.⁵⁹

These retrospective data are limited by the fact that most of the patients included did not undergo extended surgery for their disease and therefore the true benefit of adjuvant therapy in patients with stage T1b–2 disease post-radical cholecystectomy is as yet unknown. However, a retrospective study conducted at the Mayo Clinic, in which most patients underwent extended oncologic resection, did record statistically superior survival with adjuvant chemoradiation.⁶⁰ Based on these observations, it is reasonable to recommend adjuvant therapy for patients with stage II or higher GBC following surgical resection. The range of chemotherapy includes gemcitabine, fluoropyrimidines or gemcitabine-based combination chemotherapy.

In combination, these data suggest that adjuvant therapy may improve survival in patients with high-risk (T3–4, N1–2, positive margin) pathologic features. With reference to patients with node-positive disease, resected with negative margins, there is insufficient evidence at the current time to choose between adjuvant chemotherapy and chemoradiation. Although the SEER data support the use of adjuvant chemoradiation over chemotherapy alone, there is insufficient record of chemotherapy usage in the SEER database.⁶¹ Furthermore, the majority of patients included in this database underwent less than optimal surgical resections and therefore the precise benefit of adjuvant chemotherapy after margin-negative radical resection is undefined at this time. 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 is the treatment of choice in patients with R1/2 resection margins.

Role of neoadjuvant therapy in localized GBC

The role of neoadjuvant therapy in localized GBC deserves further exploration. One small study from Chile concluded that neoadjuvant therapy conferred no therapeutic advantage. However, this study predated the advent of gemcitabine-based combination regimens for biliary cancer.⁶² Moreover, the application of regional radiotherapy in non-surgically staged patients, many of whom will be found to have peritoneal or nodal disease outwith radiation portals, is not ideal. Based on the lack of data on this topic, the aggressive nature of the disease, and the morbidity of radical surgery, neoadjuvant therapy would be best applied to patients with clinical T3/T4/N1 disease on clinical trial or registry. As the Advanced Biliary Cancers (ABC)-02 trial proved that gemcitabine and cisplatin chemotherapy facilitates disease control in 80% of patients, this is currently the best regimen to apply appropriately in the neoadjuvant setting.⁶³

Treatment of patients with locally advanced and unresectable GBC

Patients with locally advanced and unresectable GBC face a dismal prognosis and suffer from morbidity resulting from biliary obstruction, pain, cachexia and infections. In this subset of patients, critical palliative manoeuvres include the maintenance of adequate biliary drainage via percutaneous or endoscopic stenting, nutritional support, pain control and management of gastroparesis. Systemic agents remain the mainstay of therapy, with gemcitabine–cisplatin chemotherapy being the treatment of choice in patients with good performance status [Eastern Cooperative Oncology Group (ECOG) status: 0–1], and single-agent gemcitabine in patients with ECOG performance status of 2. Patients with advanced GBC included in the ABC-02 trial derived significant benefit from the gemcitabine–cisplatin regimen. In patients with advanced GBC, acceptable alternative systemic therapeutic options include gemcitabine plus capecitabine.^{64–66}

Future genetic and targeted therapy

The use of targeted therapeutics represents a promising strategy for advanced GBC. Recent genomic sequencing studies have identified a host of genetic aberrations that are potentially targetable. These include *ERBB2* amplifications, mutations or amplifications of the PI3-kinase family genes, *FGFR* mutations or fusions and aberrations of the chromatin modulating genes.^{67,68} Epidermal growth factor receptor (EGFR) inhibitors like erlotinib and cetuximab have been investigated in the Phase II setting in this disease with encouraging results, but confirmatory studies are awaited before standard-of-care recommendations can be entered.^{69,70}

Consensus statements

- Given their generally poor postoperative prognosis and elevated surgical morbidity, patients with preoperatively staged T3–4 N1 disease should be considered for clinical trials studying the efficacy of neoadjuvant chemotherapy.
- Following R0 resection of stage T2 and higher N1 GBC, patients should be considered for adjuvant systemic chemotherapy and/or chemoradiotherapy.
- Patients with resected GBC with positive margins should be considered for adjuvant chemoradiation therapy.
- In patients with unresectable locally advanced and N2-positive GBC, systemic chemotherapy with gemcitabine doublets can provide effective palliation and prolong survival.

Conflicts of interest

None declared.

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