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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]

Derived from the January 2014 joint AHPBA/SSAT/SSO/ASCO Consensus Conference on the Multidisciplinary Management of Bile Duct Cancer.

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,

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 pancreatobiliary 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 Rokitansky–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 intracholecystic 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