Incidental Gallbladder Carcinoma

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Introduction

According to global cancer statistics 2018, gallbladder cancer (GBC) accounts for 1.2% of all cancer diagnoses, but 1.7% of all cancer deaths [1]. GBC is a rare yet fatal disease with poor prognosis of reported less than 5% in 5-year survival [2, 3]. Such a poor prognosis results from discovery at late stages due to vague or absent symptoms. The absence of submucosa and serosa layers between the gallbladder and the liver may have a role in the early invasion of GBC into the liver [4]. SEER cancer statistics review shows that only one in five GBC cases is diagnosed at an early stage even in a highly advanced country such as the United States [5]. Occasionally, GBC is diagnosed during or following cholecystectomy for unsuspected benign disease of the gallbladder. These cases are termed as "incidental gallbladder cancer" and present several dilemmas for further management. With laparoscopic cholecystectomy as the current gold standard for treatment of cholecystolithiasis and the most frequently performed surgical procedure worldwide for benign gallbladder diseases, the incidence of incidental GBC has also increased with some reporting up to 3% [6]. Additionally, incidental GBC is reported to be associated with more favorable pathologic characteristics such as lower tumor grade and T-stage compared to non-incidental GBC, which usually presents with concerning signs of malignancy such as jaundice and weight loss [7]. When diagnosed with incidental GBC, the current guideline recommends re-resection for T1b, T2, and T3 disease unless contraindicated by advanced disease or poor performance status [8]. However, there are still controversies in the management of incidental GBC and risk factors have not yet been fully elaborated. In this chapter, we explored up-to-date knowledge for all aspects of incidental GBC.

Epidemiology

The widespread use of laparoscopic cholecystectomy has led to the discovery of incidental gallbladder cancer at an earlier stage. GBC is discovered incidentally during histopathology following 0.25–3.0% of laparoscopic cholecystectomies [9]. This constitutes a majority of GBC diagnoses (50–70%) [7, 10]. While GBC is rare, it is the most common malignant disease of the biliary tract [11]. Incidences have been reported to vary greatly by geographical regions and ethnicity. GBC commonly occurs in South America, in countries such as Chile, Bolivia,

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and Ecuador, and in Asia, in parts of India, Pakistan, Japan, and Korea [12, 13]. Mapuche Indians in Chile demonstrate the highest rate of GBC: 12.3/100,000 for males and 27.3/100,000 for females [14]. GBC is also found in high frequency in Eastern and Central Europe, but in low frequency in Western and Mediterranean Europe, and in the United States [4]. This variation may be a result of differences in both environmental and genetic factors. In regions with a high prevalence of GBC, surgeons should practice with more vigilance to discover incidental GBC during laparoscopic cholecystectomy for presumed benign gallbladder diseases.

Risk Factors

Currently known risk factors for GBC include advanced age, female sex, polyps greater than 1 cm, porcelain GB, anomalous pancreatobiliary ductal union, and gallstones. In terms of incidental GBC, results of the American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP) database showed that the conversion of laparoscopic cholecystectomy to open cholecystectomy, advanced age (≥65 years old), Asian or African-American race, an elevated alkaline phosphatase level (≥120units/L), and female sex were independent risk factors [15]. The combination of risk factors increased the risk of incidental GBC: 6.3-fold increase for one factor, 16.7-fold increase for two factors, 30.0-fold increase for three factors, and 47.4-fold increase in risk of incidental GBC for all four factors.

Recently, the risk score model to predict incidental GBC has also been proposed based on the data from the Swedish Registry of Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (GallRiks) [16]. The model was based on five clinical variables including age, female gender, previous cholecystitis, bilirubin level, and the presence of acute cholecystitis. Risk scores were divided into low risk (<3.5 points), intermediate risk (3.5–8 points), and high risk (>8 points). Each clinical variables were given points as following: 0 for age < 60 years, 3.5 for age 60–69 years, 6.5 for age 70–79 years, 16 for age ≥80 years, 3.5 for female gender, 1.5 for previous cholecystitis, 1.5 for normal bilirubin levels/acute cholecystitis, and 2.0 for elevated bilirubin levels/no acute cholecystitis. With reference to the low-risk group, the intermediate-risk group had 3.6 times increased risk and the high-risk group had 18 times more risk of GBC.

Under the circumstances of increased risk, as previously reported, surgeons should be more attentive and prepared to perform adequate R0 resection at initial operation when incidental GBC is discovered.

Tumor Markers

Currently, there are no biomarkers for incidental GBC as tumor markers are not routinely checked for benign gallbladder diseases. For GBC, carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19–9 are most commonly utilized as tumor markers. CEA is a broad-spectrum tumor marker that is found in gastrointestinal cancer and in the normal embryonic gut, pancreas, and biliary tract. CEA level greater than 4 ng/mL is 93% specific for GBC but only 50% sensitive [17]. CA 19–9 greater than 20 IU/mL has 79% sensitivity and 79% specificity for GBC [17]. Wen et al. have shown that a combination of an elevated preoperative CEA and CA 19–9 was associated with a poor prognosis and values within normal range showed the best prognosis [18]. However, prognostic accuracy of both CEA and CA 19–9 is rather low and other markers such as CA 242 and thymidine kinase have been proposed in the past [19, 20]. Role of tumor markers and other biomarkers need to be evaluated and discovered in incidental GBC.

Diagnosis

Preoperative diagnosis of incidental GBC is difficult in clinical practice as there is no mass seen on preoperative imaging, and cholecystectomy

is performed for presumed benign stone disease. Focal or diffuse wall thickening may be present due to chronic or acute cholecystitis. Since GBC may present with wall thickening in 20–30% of cases, the differential diagnosis should be more actively sought [21].

In a study comparing non-incidental GBC and incidental GBC, sonographic characteristics showed a significantly different width of gallbladder (41.6 mm vs. 32.3 mm, $p = 0.009$, respectively) and gallbladder wall thickness (8.0 mm vs. 5.5 mm, $p = 0.016$, respectively) [22]. Incidental GBC was found with less wall thickening and smaller gallbladder width with the common presence of cholelithiasis. Findings suggested that incidental GBC has only mildly thickened gallbladder wall with difficulty in distinguishing from the inflammatory thickening. Suspicious cases of the small gallbladder with wall thickening may require further radiological evaluation to differentiate incidental GBC.

Multi-detector computed tomography (MDCT) has also been used to distinguish between benign and malignant causes of gallbladder wall thickening according to gallbladder enhancement and have reported sensitivity and positive predictive values of 75.9–82.8% and 80.0–82.8%, respectively [23]. In the study, MDCT findings of "thick" one-layer pattern with heterogeneous enhancement and two-layer pattern with "thick" enhancing inner wall $\geq$2.6 mm and "thin" weakly or nonenhancing outer wall $\leq$3.4 mm indicated signs of malignant flat gallbladder wall thickening rather than benign disease. The diagnostic accuracy of these enhancing patterns as signs of malignancy was 87.6–89.1%.

Another emerging technique for differentiating the wall thickening includes real-time elastography using acoustic radiation force impulse (ARFI). High intensity-focused ultrasound is used to evaluate the tissue stiffness in the liver, breast, and other organs [24]. Benign and malignant nodules in various organs are differentiated by using much higher stiffness present in malignant tissues due to the increased cell density compared to tissues with chronic inflammation and fibrosis [25].

Kapoor et al. [26] showed that real-time elastography diagnosed GBC with a mean shear wave velocity of 3.41 m/s [95% CI: 3.1–3.7 m/s]. With a cutoff value of 2.7 m/s, elastography showed sensitivity and specificity of 100% and 91.3%, respectively for diagnosing GBC with an overall accuracy of 92.8%. A false positive rate of 8.5% occurring in acute cholecystitis was also reported.

For suspicious wall thickening of gallbladder, routine use of elastography during ultrasonography combined with MDCT may assist in the earlier discovery of incidental GBC.

Stage Distribution at Presentation

Systemic review and meta-analysis of 2145 incidental GBC patients [27] showed that nearly half were T2 stage with a pooled proportion of 47.0% (95% CI: 0.421–0.519) at presentation. T1 and T3 were discovered at similar rate with pooled proportion of 23.0% (95% CI: 0.178–0.291) for T1 and 25.1% (95% CI: 0.195–0.317) for T3. Pooled proportion of lymph node metastases was 14.2% (95% CI: 0.107–0.185). Results of a multicenter study on 724 GBC cases by the French Surgical Association showed that 85% of cases were identified as T3 or T4 [28]. While GBC is usually discovered at an advanced stage, incidental GBC is diagnosed at an earlier stage. With early diagnosis, prognosis is greatly influenced. The 5-year overall survival rate for T1a and T1b is over 95% [29] and for T2 is 70% [30]. In order to increase the survival of GBC, efforts to discover more incidental GBC may be essential.

Pathologic Examination and Staging

Pathologic examination is important for appropriate staging and further management. Yet, no consensus has been met on a uniform pathologic examination protocol for those with no clinical or imaging suspicion for GBC and no apparent abnormality on gross examination. Due to limited resources and low risk of cancer, some

centers do not recommend a microscopic examination in these situations [31]. However, results from GallRiks data showed that routine pathologic examination rather than selective uncovers a higher proportion of incidental GBC [32]. The current guideline suggests a routine histopathological examination of gallbladder specimens including minimal microscopic evaluation of three sections and the cystic duct margin, particularly in areas of high incidence [8].

Once a diagnosis is confirmed as GBC, correct staging according to the depth of invasion is critical in establishing further treatment. (Table 1) Staging influences disease management and prognosis. Current AJCC 8th cancer staging manual [33] for gallbladder cancer contains several changes from the previous edition. First, the T2 category (stage II) was separated into T2a (stage IIA) and T2b (stage IIB), depending on the tumor location on peritoneal or hepatic side of the gallbladder, respectively. This change was based on results from a multi-institutional study showing worse survival after resection of T2 GBC on the hepatic side of the gallbladder [34]. Second, the N category has been changed from an anatomic location-based system to a number-based system. Regional metastatic lymph nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein are classified into N1 and N2 stages, depending on the involvement of 1–3 LNs and $\geq$ 4 LNs, respectively. Periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes are now classified as distant metastasis. Finally, retrieval of at least six lymph nodes is recommended in patients with T1b or greater.

Restaging Prior to Re-Resection

After the diagnosis of GBC has been confirmed, appropriate staging workup should be undertaken to exclude disseminated disease or obvious early recurrence. Patients should undergo chest and abdominal CT as a minimum requirement for restaging and consider other imaging modalities such as MRI and PET for selected cases based on features on CT or MRI.

In a retrospective Surveillance, Epidemiology and End Results (SEER) database study, CT scan was the most utilized perioperative imaging modality [35]. MRI can also be used to detect vascular invasion, biliary tract involvement, liver

Table 1 TNM staging according to AJCC 8th edition

Stage group	T category	T-criteria	N category	M category
0	Tis	carcinoma in situ	N0	M0
I	T1a	Invades lamina propria	N0	M0
	T1b	Invades muscular layer	N0	M0
IIA	T2a	Invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa	N0	M0
IIB	T2b	Invades the perimuscular connective tissue on the hepatic side, with no extension into the liver	N0	M0
IIIA	T3	Tumor perforates the serosa or directly invades the liver or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum or extrahepatic bile ducts	N0	M0
IIIB	T1-3		N1	M0
IVA	T4	Invades the main portal vein or hepatic artery or invades two or more extrahepatic organs or structures	N0-1	M0
IVB	Any T		N2	M0
	Any T		Any N	M1

*N1: 1–3 regional lymph node metastases, N2: 4 or more regional lymph node metastases

invasion, and lymph node involvement with reliable accuracy [36].

The role of PET-CT has not been sufficiently proven in a prospective fashion for patients with GBC; however, numerous retrospective studies have reported some utility. In a study from Memorial Sloan Kettering Cancer Center, PET results altered the management of 23% of GBC patients [37]. A study evaluating 108 patients undergoing PET before re-resection found that PET was useful in stratifying patients for effective treatment and significantly higher uptake was associated with residual disease [38]. PET was also reported useful in the assessment of local residual disease in T1b GBC [38]. If there is no uptake in PET for T1b, re-resection was not recommended due to the low risk of residual disease.

Surgical Strategy

Reoperation for incidental GBC should have two fundamental objectives: R0 resection and clearance of the locoregional lymph nodes.

For tumor contained within the mucosa (Tis or T1a), cholecystectomy alone is sufficient for complete R0 resection as the risk of lymph node dissemination is low. With negative resection margins, 5-year survival after simple cholecystectomy is reported between 99% and 100% with a less than 2% risk of lymph node involvement [39]. However, great care should be exercised to prevent bile spillage during operation. If the surgeon cannot guarantee an adequate resection without spillage during laparoscopy, open cholecystectomy should be considered.

For T1b GBC, current guidelines recommend extended resection with lymphadenectomy because of the possibility of nodal involvement in about 10% [39, 40]. However, there are controversies in the necessity of re-resection in T1b GBC. According to National Comprehensive Cancer Network Guidelines 2019, for T1b and greater, postoperative workup including CT and MRI along with consideration for staging laparoscopy are recommended. In cases of resectable state, hepatic resection and lymphadenectomy are recommended with bile duct resection when needed. For unresectable cases, chemotherapy, radiation therapy, and/or best supportive care are recommended [41]. While NCCN guidelines recommend a more radical approach to T1b, the results of a systemic review found no definite evidence that extended cholecystectomy provides a survival benefit over simple cholecystectomy in T1b GBC [39]. Nevertheless, since the lymph node metastasis is considerable (10%), regional lymphadenectomy should be performed for the treatment and staging of GBC.

T2 GBC is often diagnosed incidentally after laparoscopic cholecystectomy and it is well known that 5-year overall survival is superior when re-resection with extended cholecystectomy is performed (55–90% vs. 0–40%) [42, 43]. Extended cholecystectomy includes resection of the gallbladder bed and hepatectomy to achieve an R0 resection; a 2–3-cm margin is commonly used. The extent of liver resection ranges from partial hepatectomies (nonanatomical or anatomical resection of segments 4a and 5) to major extended hepatectomies. Anatomical resection of segments 4a and 5 is considered a good oncologic option for GBC because the cystic vein drains into segment 4a (37–90%) and segment 5 (52–90%) [44, 45]. A more radical method of routine right extended hepatectomy including caudate lobectomy has also been proposed. However, results have not shown improved survival for major resection over nonanatomical liver resection and increased morbidity has been associated with major resection [46, 47]. Consequently, complete R0 resection with limited liver resection is the recommended approach to GBC, as long as negative margins are achieved.

With the newly introduced subdivision of T2 based on the tumor location, there are recent debates on the necessity of extended cholecystectomy for all peritoneal side T2 GBC [48]. The presence of residual disease in incidental GBC has been reported to be 57–70% for T2 and 77–91% T3 [49, 50]. Residual disease has a profound impact on survival. Patients without residual disease after re-resection had a better

5-year survival than those with residual disease (84.8% vs. 36.9%, p = 0.01) [50]. In order to better predict the risk of residual disease, Ethun et al. [51] proposed the gallbladder cancer predictive risk score (GBRS) based on T-stage, tumor differentiation, lymphovascular invasion (LVI), and perineural invasion (PNI). Each pathologic characteristic was assigned a following value: T1a-0, T1b-1, T2–2, T3/4–3, well-diff-1, mod-diff-2, poor-diff-3, LVI-negative-1, LVI-positive-2, PNI-negative-1, PNI-positive-2. The values were added and separated into three risk groups including low risk (3–4), intermediate risk (5–7), and high risk (8–10). In the high-risk group, chances of locoregional residual disease were estimated to be 61% and re-resection is necessary if possible. For intermediate-risk group, the risk of locoregional residual disease is estimated to be 24% and re-resection should be aggressively pursued. In the low-risk group, however, re-resection may not be necessary with low chances of residual disease. The approach to incidental GBC is still controversial because of the difficulty in comparing data derived from nonuniform case studies. Application of GBRS may be limited in the current form because of a limited number of patients evaluated for developing the scoring system. However, with further validation in a larger population, GBRS may prove to be a great tool in optimizing the treatment strategy.

Intraoperative Findings

Events during the operation may influence oncologic outcome and treatment strategy. In a result based on German registry, intraoperative gallbladder perforation resulted in significantly higher local recurrence rate (38.4% vs. 27.2%, p = 0.047) [52]. Gallbladder perforation or bile spillage during operation has been associated with poor oncologic outcomes and increased risk of peritoneal carcinomatosis [53–57]. Ouchi et al. [54] reported that gallbladder perforation during laparoscopic cholecystectomy was found in 94 of 470 patients (20%). Risk factors associated with gallbladder perforation is not clear but increased T stage and severity of inflammation may cause greater difficulty during operation, leading to higher chances of intraoperative gallbladder perforation. In acute cholecystitis, severe gallbladder inflammation such as emphysematous and gangrenous cholecystitis is highly associated with gallbladder perforation [58]. While the association between intraoperative gallbladder perforation and inflammation in gallbladder cancer has not yet been found, preoperatively elevated neutrophil–lymphocyte ratio (NLR > 5) [59] and presence of inflammation [60] were found to be associated with poor oncologic outcome after curative resection for GBC. Utmost care to prevent bile spillage and gallbladder perforation is indisputably necessary during operation.

Perioperative Therapy

Role of adjuvant chemotherapy in GBC has not yet been fully elucidated. The majority of recurrences after resection of GBC was found to be distant, emphasizing the systemic nature of GBC and the need for multimodal therapy [61]. In a series of incidental GBC, adjuvant chemotherapy has been shown to be associated with better survival [7]. A meta-analysis of 6712 patients also supported the use of adjuvant therapy after surgery for biliary tract cancers [62]. Until recently, a combination of cisplatin and gemcitabine has been preferred regimen based on the Advanced Biliary Cancer (ABC)-02 trial, which demonstrated in a randomized controlled trial of 410 patients with advanced biliary tract malignancies (149 patients with GBC) [63]. Results showed an overall survival of 11.7 months for cisplatin plus gemcitabine versus 8.1 months for gemcitabine alone. However, the overall application was less than 30% and treatment benefit was small [64]. A recent BILCAP (BILiary CAPecitabine) randomized controlled trial in 447 patients showed that 6 months of adjuvant capecitabine improved overall survival compared to placebo [65]. Thus, this regimen is currently recommended after the re-resection of incidental GBC [66]. Current

guidelines and consensus statements recommend adjuvant chemotherapy for any T2 disease and above with N1 disease, given the high risk of recurrence and nodal involvement [8, 67].

In terms of radiotherapy, the utility in adjuvant setting has not been proven. There are no randomized trials for radiotherapy and is only performed in some centers. Currently, chemoradiation is recommended only in microscopically positive surgical resection margin (R1 resection) [66]. There is no evidence for the use of neoadjuvant therapy prior to re-resection.

Conclusion

GBC is a rare yet fatal disease. Most cases are discovered incidentally while treating a benign disease, indicating the importance of surveillance during laparoscopic cholecystectomy. Incidental GBC is generally diagnosed at an earlier stage and carries a better prognosis than nonincidental GBC. Therapy can be multimodal yet surgical intervention is the mainstay of GBC treatment. A simple cholecystectomy is adequate for GBC contained within mucosa (Tis, T1a). For T1b and above, reoperation for incidental GBC should have two fundamental objectives: R0 resection and clearance of the locoregional lymph nodes. The role of adjuvant therapy needs further investigation in better detail and for subgroups. Until then, adjuvant capecitabine seems to improve oncologic outcomes. Due to the rarity of the disease, efforts to recruit patients into ongoing multicenter clinical trials and further prospective studies are warranted for a better understanding of incidental GBC.

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