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Review Article

Minimally invasive surgery for gallbladder cancer

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Abstract

Minimally invasive surgery (MIS) for gallbladder cancer (GBC) has been increasingly performed, including an increasing number of reports of radical cholecystectomy with hepatectomy, lymphadenectomy and excision of the extrahepatic biliary tree, but continues to be controversial. Here, we highlight these controversies and review the management of incidental GBC, and the MIS management of early and advanced nonincidental GBC. While initial results are promising, and are likely to improve, adequate long-term survival data are lacking and for now MIS for GBC should be limited to high-volume centers with adequate expertise in both MIS and hepatobiliary surgery.

Keywords: minimally invasive surgery; gallbladder cancer; radical cholecystectomy; hepatectomy

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Introduction

Whereas minimally invasive surgery (MIS) found one of its first and most widely adopted applications in the

treatment of benign gallbladder disease, its application to gallbladder cancer (GBC), a much less common disease, has only relatively recently developed. While GBC is uncommon among gastrointestinal cancers [1], it is one of the most common cancers of the biliary tract [2] with most (about 50%-70%) of GBC cases discovered incidentally upon pathologic review (0.2-2.1% of all cholecystectomies for presumably benign disease) [3-6]. It is significantly (1.7 times) more common in women than men and the incidence among these women has not appreciably decreased since the 1990s [1]. The American Cancer Society estimates approximately 4,000 new GBC cases in 2017 in the U.S.A [7].

GBC is more prevalent in certain geographical regions and ethnic groups, such as South American, Native American, Mexican, Indian, Pakistani, Japanese, and Korean populations [8, 9, 2], which may be explained by dietary habits and genetic predisposition. It is also associated with chronic inflammation secondary to liver fluke (eg, Clonorchis sinensis) and chronic infection by Salmonella typhi, S. paratyphi, Helicobacter bilis and H. pylori, as well as with some medications and environmental exposures [2]. Congenital biliary-tree abnormalities such as choledochal cysts or pancreaticobiliary maljunction are also known GBC risk factors [8]. Cholelithiasis, however, is the most important GBC risk factor, with a relative risk of 4.9 [2].

Unique morphological features of the GB, such as an absent submucosa, a thin muscularis propria, Rokitansky-Aschoff sinuses, and lack of peritoneal coverage on the liver side, may all contribute to early invasion and dissemination of GBC, and partly explain its aggressive nature and the poor survival of these patients. Not only does this have implications for MIS, to be discussed below, but these features may also be responsible for some common pitfalls in gross and histopathologic examination, leading to inaccurate determination of the depth of invasion and disease understaging. Indeed, in more than half of cases of early GBC - those cases most readily amenable to MIS - the tumor is grossly unapparent to the pathologist [10].

Gallbladder cancer is commonly staged using the AJCC 7th edition: Tis (without invasion of the basement membrane), T1a (invasion into the lamina propria), T1b (invasion in the muscularis layer), T2 (invasion into perimuscular connective tissue but not beyond the serosa or into liver), T3 (perforation of serosa and/or liver invasion and/or adjacent organ or structure), T4 (invasion into the main portal vein, hepatic artery or more than one structure beyond the liver). Based on data collected in the 1990s, predating MIS, the 5-year overall survival by GBC stage reflects its aggressive nature: Stage 0 = 80%; I = 50%; II = 28%; IIIA = 8%; IIIB = 7%; IVA = 4%; IVB = 2% [11]. Some more recent literature does not reflect significant improvement, with reported overall 5-year-survival rates for even early GBC varying widely, from 40% to nearly 100% [12, 13]. Unfortunately, due to silent nature of the disease, less than 20% of patients are considered surgical candidates at the time of presentation. Those who do undergo R0 resection have a 5-year

survival of only 21-69% [8] .While some studies have suggested that this grim status has not appreciably improved over the past 15 years [14]. Other, more recent studies show some measurable but modest improvement over time [1].

Surgical treatment of GBC depends on the stage, with Tis and T1a lesions being largely curable with simple cholecystectomy, which is typically done laparoscopically or robotically. T2 cancers are typically treated with extended cholecystectomy, which includes the gallbladder bed (either as a nonanatomic wedge or a segmental resection, ideally en bloc with the gallbladder), a lymphadenectomy, and, if the cystic duct margin is positive, an excision of the extrahepatic biliary tree (EHBT). T3 lesions are often treated with extended cholecystectomy and a major hepatectomy (>2 segments). Most T4 cases are unresectable and are treated palliatively. Adjuvant chemotherapy is applied on a case-by-case basis in consultation with medical oncology, but is not particularly effective.

Because the application of MIS for GBC requires the same oncologically sound approach as for open cases, any would-be MIS surgeon treating GBC must be well versed in several controversies regarding the surgical treatment of GBC.

Controversies Regarding MIS for GBC

MIS as an Approach - Overview

Although MIS has been adopted for the surgical treatment of different types of GI cancers, its application to GBC traditionally has not been recommended when preoperative suspicion for GBC is high. Most consensus guidelines, including National Comprehensive Cancer Network (NCCN) and the Japanese Society of Hepato-Biliary-Pancreatic Surgery, are either noncommittal or recommend against MIS [15, 16]. However, these guidelines are partly based on historic-era data (before 2000) and largely on the relatively small case series.

The rationale for criticism of MIS for GBC is based mainly on a higher risk of spillage of gallbladder bile (which is laden with cancer cells); this may occur when the gallbladder is perforated, which occurs in up to 40% of high-risk cases [17]. Spillage essentially invariably leads to peritoneal dissemination [18, 19]. Additional concerns include the technical difficulty of radical cholecystectomy, especially the ability to effect a resection that is as oncologically sound as the standard open approach, including the ability to perform an adequate hepatectomy, lymphadenectomy, and if needed for a positive cystic-duct margin, an excision of the EHBT, all of which require very advanced MIS skills. Although initial reports of MIS for GBC uniformly show low 30-day morbidity and mortality, one must be wary of publication bias. Furthermore, a recent study of National Cancer Database data on MIS for GBC revealed that the full weight of the mortality may not be appreciated at 30 days, given that the 90-day mortality was 2.3 times the 30-day mortality [20].

MIS and Incidental Gallbladder Cancer

Since incidental GBC (iGBC) tends to be found at an earlier stage than symptomatic GBC, the main controversy

here regards the management of those early cases in the T1b category. This is discussed in detail below, but suffice it to say that the most important point in the management of iGBC is its prevention, ie, its avoidance by the surgeon having a high index of suspicion prior to the presumably routine cholecystectomy for what turns out to be GBC, viz, for iGBC. Recent work by our group [19] and others [21-23] has identified several risk factors that may clue the surgeon to the fact that what at first seems to be routine benign gallbladder disease may in fact be iGBC, the recognition of which may avoid not only the morbidity associated with a likely reoperation for completion extended cholecystectomy but also the increased risk for carcinomatosis in case of bile spillage. These risk factors include surgeon decision for an open as opposed to MIS cholecystectomy, older patient age, elevated alkaline phosphatase and dilated bile ducts, and the presence of gallbladder wall thickening, especially in the absence of pericholecystic fluid [19, 21-23].

MIS and Treatment of T1b GBC

While the surgical treatment, regardless of approach, for Tis-T1a and for ≥T2 lesions is relatively straightforward, the optimal operation for T1b lesions has been traditionally considered controversial [24]. However, with the recent publication of National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology [25] and other expert consensus statements [26], most hepatobiliary surgeons and surgical oncologists agree that T1b cancers should be treated with extended cholecystectomy as for T2 lesions, since up to 10% of cases will harbor residual disease.

MIS and Routine Excision of Extrahepatic Biliary Tree

Several groups, especially in Japan, have long recommended routine excision of the EHBT regardless of stage, in order to better prognosticate early-stage patients and to completely extirpate malignant lymph-node-bearing tissue along the EHBT [27, 28]. As noted by Miller and Jarnagin, however, there is little evidence to support this approach [29]. The NCCN guidelines leave this decision open to surgeon discretion for both iGBC and for non-iGBC unless jaundice is a presenting symptom in which case likely invasion of the bile duct warrants excision of the EHBT in otherwise resectable cases [25]. Even in the absence of jaundice, EHBT excision should be performed when the cystic-duct margin in positive [30]. More recent series [31, 32], as well as a recent systematic review [33], have suggested that routine excision of the EHBT increases only morbidity, not survival.

MIS and Radical Resections: Extent of Lymphadenectomy and Hepatectomy

While some Japanese groups have advocated for radical resection even for early GBC, including extended right hepatectomy, extended aortocaval lymphadenectomy, portal-vein resection, and even pancreaticoduodenectomy [34-36], citing improved survival, this improvement has not been widely reproduced and is not advocated by most North American and European groups, citing worse morbidity without concomitant survival advantage [37, 32, 30].

MIS and Port-Site Recurrence

The rate of port-site recurrence (PSR) after laparoscopic cholecystectomy for GBC varies from 14-30% in the pre-2000 historic era [38] to 10.3% after 2000, the extraction site being at significantly higher risk than other trocar sites [39]. PSR usually occurs within 6-10 months after resection and is characterized by a poor 1-year survival [40, 38].

Mechanisms theorized to lead to PSR include direct contamination with malignant cells during specimen extraction, particularly in cases of bile spillage, contamination of instruments by tumor cells, and the so-called "chimney effect," in which aerosolized tumor cells may pass with leaking pneumoperitoneum along trocars to be deposited in the abdominal-wall port sites [8].

Resection of port sites was traditionally recommended during surgical treatment of iGBC. However, this practice has more recently been challenged since, while PRS does bode a poor prognosis, resection of port sites does not seem to affect survival [41-43].

Diagnostic Staging Laparoscopy

In the predominantly open era, the use of diagnostic staging laparoscopy (DSL) to avoid a nontherapeutic laparotomy in cases of carcinomatosis not appreciated on preoperative imaging was controversial. Although this "controversy" has been increasingly rendered moot due the increasing use of MIS resections, it still warrants mention because even for the non-MIS surgeon planning an open operation, there is increasing agreement that DSL is warranted prior to open cases.

Despite extensive preoperative imaging, peritoneal and liver surface metastases, may be missed, even with the best available imaging. Up to 56% of patients have been spared a nontherapeutic laparotomy with this approach [44], which is now widely accepted prior to laparotomy in patients at high risk for peritoneal and liver surface metastases, such as those the ≥T3 lesions, poorly differentiated cancers, positive gallbladder margin, or other high-risk factors [45, 44, 30].

MIS Management of iGBC

The discovery of iGBC occurs typically upon review of final pathology postoperatively, but may occur intraoperatively by frozen-section biopsy. The surgical management of iGBCa depends not only on which of these two ways it is discovered, of course, but also on the T stage of the tumor and on the patient's comorbidities. Since an oncologically sound (re)operation may be required, several points need to be understood before one embarks on resection, regardless of the approach.

iGBCa Discovered Postoperatively

In this most common scenario, the surgeon must review the pathology report in detail, and should in addition consider discussing the case directly with the pathologist, to ensure that what can be known is known. In particular, the T stage, the status of the cystic-duct margin, and the location of the tumor on the gallbladder should be determined, if possible. The T stage, as discussed above, is essential since this is the major determinant of the extent of resection that will be required. In addition, the status of the cystic-duct margin should be clearly defined as involving or being free of involvement by cancer or

high-grade dysplasia [46]. Regarding the location of the tumor, both the lateral location (ie, free peritoneal side versus liver bed side) and the vertical location (fundus versus body versus infundibulum) should be determined, if possible, although the vertical location is more important since a low-lying cancer is more likely to involve the cystic-duct margin. Because ~99% of cases do not have iGBCa, however, little attention is typically paid to orientation of the gallbladder during grossing and sectioning for review by the pathologist, and so this information is often not available.

In addition to the pathology report, the operative course during index simple cholecystectomy should be reviewed with emphasis on intraoperative bile spillage and the use of specimen-retrieval bag. Intraoperative bile spillage is associated with development of peritoneal carcinomatosis, which carries a dismal prognosis [19, 47].

Having reviewed the pathology and operative course, staging workup should be performed, including chest imaging, abdomen and pelvis CT scan to assess for presence of enlarged para-aortic lymph, assessment of vascular and biliary involvement and presence of distant metastasis and tumor markers (CA19-9 and CEA) [25].

Reoperation is indicated for in cases staged T1b and greater. Whether reoperation is to be approached with MIS of with an open operation, a diagnostic laparoscopy should be strongly considered before proceeding with the required resection. This should include assessment of deep liver lesions with laparoscopic intraoperative US, of residual disease in the gallbladder fossa, of local and para-aortic lymphadenopathy especially assessment for aortocaval lymphadenopathy after performance of a laparoscopic Kocher maneuver (recommended by some but not all experts), and of the presence of peritoneal disease, which we have observed to develop in as little as 30 days from bile spillage at laparoscopic cholecystectomy[25]. Consistent with this observation, some authors have advocated delaying reoperation for a period of 3 months[48, 49] to identify patients at high risk for not benefiting from MIS or open extended resection due to evidence of disease progression in the this time interval. Such patients include those with bile spillage and with higher T stage, especially T3.

iGBC Discovered Intraoperatively

If iGBC is suspected intraoperatively, the suspicious area of the excised gallbladder should be clearly marked and communicated directly to the pathologist, and sent for frozen-section biopsy. Laparoscopic staging should be performed as described above. Frozen section has accuracy of 86% to 95% in determining T stage [50, 51]. If the disease is resectable, the surgeon’s expertise adequate, and the patient's fitness for a major operation appropriate, then proceeding with an MIS curative-intent operation is reasonable. We typically inform the patient during informed consent that a major operation may be required, even when GBC is very unlikely, since a major bile-duct injury may also require a major operation. If adequately comfortable MIS skills are lacking, then referral to an MIS HPB surgeon ideal.

Table Minimally invasive radical cholecystectomy for gallbladder cancer

Author; Year[ref]	N	MIS --> Open	Extent of LR	LAD; Extent	EHBT	IOUS	Completion: Elective	Stage	5YS
Cho; 2008[58]	3	0	NAW, 2 cm	Y; 4	N	Y	0:3	T1a: 1 T2:2	NR
Gumbs; 2010[59]	3	0	NAW, 3-5 cm	Y; 3	N	Y	1:2	T1b: 1	NR
de Aretxabala; 2010[60]	17	13	NAW, NR	Y; 6	N	NR	17:0	NR	NR
Belli; 2011[61]	4	0	NAW, NR	Y; NR	N	Y	4:0	Tis: 1 T1b:3	NR
Shen; 2012[62]	5	0	NAW, 2cm	Y; 9	N	Y	2:3	T2: 2 T3: 3	NR
Gumbs; 2013[63]	15	1	NAW, 1-3 cm	Y; 4	Y (1 case)	Y	5:10	T1b: 8 T2: 4 T3: 3	NR
Machado; 2015[57]	1	0	Seg 4B and 5	Y; 9	N	N	1:0	T1b	NR
Yoon; 2015[54]	45	1	NAW, NR	Y; 7	N	Y	0:32	Tis: 2 T1a: 10 T1b: 8 T2: 25	94.2% (DS)
Shirobe; 2015[64]	11	0	NAW, 1 cm	Y; 13	Y (2 cases)	N	7:4	T1b: 3 T2: 8	T1b: 100% T2: 83.3%
Agarwal; 2015[65]	24	0	NAW, NR	Y; 10	N	N	4:20	T1a: 4 T1b: 1 T2: 11 T3: 8	NR
Itano; 2015[55]	16	0	NAW, 1 cm	Y; 12.6	N	Y	0:16	T1a:1 T1b: 2 T2: 13	NR
Palanisamy; 2016[66]	14	0	Seg 4B and 5	Y; 8	N	N	0:14	T2: 11 T3: 1 Benign: 2	68.8% (O)

Abbreviations: EHBT, extrahepatic biliary-tree excision; IOUS, intraoperative ultrasound; LAD, lymphadenectomy; LR, liver resection; NAW, nonanatomic wedge; NR, not reported; O, overall survival; Seg, segment

MIS Management of Preoperatively Detected Early GBC

The most common presentation of preoperatively detected GBCa is the presence of a mass on imaging, done either for symptoms referable to the mass or for reasons unrelated to the mass. In either case, as described above, surgical treatment depends on the stage. Interestingly, patients with non-iGBCa have significantly worse survival than those with iGBCa, even when stratified by stage [6, 37].

Only very recently has the surgical dogma of strongly recommending against MIS for GBCa been challenged. Although it may still be too early to conclude that this challenge has been successful, increasing numbers of reports claim equal oncologic outcomes, although the quality of these data is generally low, and follow-up is short, with most series not reporting 5-year survival (Table). One of the largest series to date (not included in the Table) is a multi-institutional Korean study of 94 laparoscopic cholecystectomies, 77 stage T1a and 17 stage T1b [13]. In this study, compared to patients who underwent open simple cholecystectomy, those undergoing laparoscopic simple cholecystectomy had similarly excellent 5-year survival (100% and 95%, respectively), and simple and extended cholecystectomy had similar 5-year survival for T1a (97.4% vs 100%) and T1b (95.7% vs 100%) tumors. But the authors did not compare survival between T1b tumors treated open vs laparoscopically.

MIS Management of Preoperatively Detected Advanced GBC

In order to select the patients for radical MIS resection of advanced GBCa, careful preoperative evaluation is essential. Diligent review of high-quality, multiphase, axial imaging is of paramount importance, paying particular attention to the local extent of the tumor, lymph-node enlargement, the presence of distant metastasis, vascular involvement, and biliary-tree dilatation. This will help the surgeon to determine the likelihood of performing an R0 resection and the feasibility to employ MIS to this end. It also helps the surgeon to determine the extent of liver resection required, need for biliary resection and reconstruction and if any adjacent organs need to be included in the resection. In addition, preoperative endoscopic ultrasound likely provides a useful adjunct to axial imaging and may be used liberally to assess the tumor along with assessment of depth of invasion [52-55]. Preoperative imaging findings associated with an unfavorable risk/benefit ratio, and therefore typically rendering the tumor unresectable, include: 1) Enlarged N2 lymph nodes, (aortocaval, celiac, periduodenal, peripancreatic, and superior mesenteric artery nodes); 2) Involvement of the main portal vein or hepatic artery, which constitutes T4 disease, and which, despite being technically resectable, has such a poor prognosis as to be prohibitive; and 3) The presence of peritoneal disease and distant metastasis[26].

Intraoperatively, a thorough diagnostic laparoscopy is recommended prior to attempted resection and this should include evaluation for peritoneal disease and N2 nodes. Any suspicious

lesion or node should be biopsied and sent for frozen section. Facility with laparoscopic intraoperative ultrasound is essential to assess for liver metastasis, to assess depth of liver invasion by the tumor, and to plan the anticipated liver resection by mapping the major vessels intraparenchymally. Type of probe is surgeon-dependent, but we prefer a flexible probe over the rigid probe to facilitate examination of the dome and to move more easily from longitudinal to transverse views of major structures and lesions.

Radical cholecystectomy with en bloc hepatectomy is performed, but there is no general consensus regarding the amount of liver resection. Our preference is to excise a 2-cm wedge of segments 4b and 5, generously encompassing the gallbladder, and cystic plate in situ, although some authors recommend an anatomic bisegmentectomy 4b/5 [56, 57]. Frozen section is then performed to confirm carcinoma, negative cystic-duct margin and a negative liver margin. Portal lymphadenectomy is performed and some authors extend this to N2 nodes. If the cystic-duct margin is positive, then bile-duct resection is required, typically followed by a Roux-en-Y hepaticojujenostomy reconstruction. At any point during the operation, the surgeon should not hesitate to convert to an open approach if persistence with MIS is deemed likely to compromise an oncologically sound, complete R0 resection.

Conclusion

MIS for radical resection of GBCa is safe and technically feasible in skilled hands, but cannot at this time be recommended as a standard of care but rather should be limited to high-volume specialized centers with available expertise. The surgical management with MIS should very closely mirror that of open surgery and the adoption of MIS must not compromise the ability to perform an R0 resection with liver resection, portal lymphadenectomy and along with possible biliary-tree resection and reconstruction.

Conflict of interest

The authors have no potential conflicts of interest to disclose.

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