Incidental Gallbladder Cancer Post Laparoscopic Cholecystectomy

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Introduction

Gallbladder cancer is the commonest malignancy of the biliary tract, and the fifth most common gastrointestinal cancer [1, 2]. However, it is a rare condition, with the annual incidence in the USA quoted at 3 per 100,000 [3]. Hence, general surgeons encounter advanced (T3 and T4) gallbladder cancers only occasionally. The prognosis is poor, as the disease is often advanced at diagnosis and only resectable in 25% of patients [4, 5]. It behaves aggressively, reflected in a median overall survival of 3–11 months, and 5 year survival of 3–13% [4]. However there is variation in survival within different clinical stages [6, 7]. Detection in earlier stages may result in prolonged survival [8], a situation relevant to the scenario of incidental gallbladder cancer (IGBC) [9, 10].

Gall bladder cancer is not evident on preoperative imaging or intraoperatively in 15–30% of patients and IGBC is detected in 0.3–2% of patients undergoing a LC [2, 10–13]. In fact about two thirds of patients with potentially curable gall bladder cancer are picked up as IGBC [3]. These facts, coupled with the widespread prevalence of LC, results in the general surgeon facing a situation of either:

1. finding gall bladder cancer incidentally in the operative specimen on histology
2. faced with a suspicion of gall bladder cancer intraoperatively.

This chapter discusses and outlines the course of action to take in these two scenarios.

Post Laparoscopic Cholecystectomy Detection of Gall Bladder Cancer on Histology

Initially, the histology report needs to be carefully reviewed for correct staging of the malignancy. This requires the assessment of the depth of invasion into the gall bladder wall (T staging) (Table 14.1), and whether the cystic duct margin is involved. Following this assessment imaging to stage the gallbladder cancer is necessary (see later), in particular if these have not been staged preoperatively (which is most likely), or if there is a gap between the cholecystectomy and further treatment. Twenty percent of patients requiring revisional surgery were found to have

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unresectable disease at the time of revisional surgery [14].

Prognosis depends mostly on the T-stage (Table 14.1) of the tumour. The 5 year survival rate following LC for IGBC are: T1 cancers 92%, this falls to 59% for T2 cancers [15]. Spillage of gallbladder bile during the LC increases the risk of peritoneal dissemination and port site recurrence, and impacts adversely on survival [15]. Gall bladder perforation at laparoscopic cholecystectomy results in port site recurrence of up to 40% [16]. Thus, it is important to know whether the gallbladder was perforated during the index operation.

Stage Tis and T1a gall bladder cancers do not require any further surgery, as the cholecystectomy would be curative, provided there was no intra-operative spillage of gallbladder bile, and the gall bladder was extracted using a bag. The low rate of lymph node metastases (2%), and recurrence rate (1%) in this group is low enough to suggest that LC alone is very likely to be curative and no further treatment is indicated [17]. LC for T1a disease has an excellent reported 5 year survival of 100% [18].

Stage T1b, T2 and more advanced tumours (in the absence of metastatic disease) warrant further surgery, in the form of immediate re-resection. At re-resection, the gallbladder bed segments 4b and 5 of the liver are resected (non-anatomical wedge resection of at least 2–3 cm), lymphadenectomy of the hepatoduodenal ligament and sampling of the cut end of the cystic duct is done. If there is evidence of malignancy at the cut end of the cystic duct margin, further excision of the cystic duct is performed. If complete clearance on the cystic duct margin cannot be obtained, excision of the bile duct is indicated. Hepatectomy and radical bile duct excision are rarely required, provided negative surgical margins are attained. Resection of port sites was widely practiced at the time of re-resection, but more recent data has not shown any survival benefit [19].

Table 14.1 TNM staging of gallbladder cancer

TNM stage	Histological invasion	Stage
Tis	Carcinoma in situ	0
T1 T1a T1b	Gall bladder wall Lamina propria muscle	I
T2	Perimuscular connective tissue	II
T3	Serosa, one organ and liver	IIIa
T4	Portal vein, hepatic artery, or two or more extrahepatic organs	IVa
N1	Regional lymph node metastases (adjacent to gall bladder)	IIIa
N2	Lymph nodes beyond hepatoduodenal ligament (periaortic, pericaval, SMA, celiac)	IVb
M0	No evidence of distant metastases	
M1	Evidence of distant metastases	IVb

Five year survival following radical surgery for T1b lesions is 60–100%, while it ranges between 54% and 100% for T2 cancers [20–22]. Lymph node metastases occur in 11% of T1b lesions, and the recurrence rate is 9%. There some debate as to whether simple cholecystectomy versus radical excision should be practiced in T1b tumours. Radical cholecystectomy is recommended for T1b tumours by the National Comprehensive Cancer Network [23] and immediate re-resection results in a threefold reduction in recurrence in T1b tumours [24]. In T2 tumours, immediate re-resection allowed for better staging and in node negative disease, resulted in better survival [25].

Fortunately, most IGBC are T1 or T2 lesions. The treatment of locally advanced gall bladder cancer (T3 and T4 disease) is challenging, with poor 5 year survival of 0–32% [26]. The survival benefit from surgery is offset by the morbidity and mortality associated with major surgery [27]. Hence, curative surgery should only be attempted if R0 resection can be obtained. Recent improvements in preoperative staging and anaesthetic techniques have permitted aggressive surgery in T3 and T4 lesions, with improved survival [28, 29]. In addition to the T stage of the tumour, nodal status also impacts hugely on outcome. Node negative disease patients, following radical resection, have a 5 year survival of 58–77%, in contrast to the dismal 0.45% in node positive patients [30, 31].

Intra Operative Suspicion of Gall Bladder Cancer

It is not easy to detect gall bladder cancer intraoperatively if it is an early (T1 or T2) lesion, or there are signs of either acute or chronic inflammation masking the underlying malignancy. A clinical diagnosis of empyema, and patient age over 60 years are two risk factors for the diagnosis of IGBC [32]. Twenty five percent of gall bladder cancers can present with imaging features of acute/chronic cholecystitis, with the diagnosis of malignancy evident in 1% of these patients [33]. Other features on CT that should raise concern for malignancy are lymphadenopathy, extensive wall thickness or focal thickness, and reduced distension of the gall bladder [33].

Suspicion of gall bladder cancer at the time of cholecystectomy would arise of the GB is hard, abnormally thickened [34] or there is infiltration of the liver. If there is any suspicion of gall bladder cancer, a decision needs to be made regarding stopping the operation or continuing with a cholecystectomy and risking compromising the outcome if gallbladder cancer is actually present versus performing a cancer type resection (including liver resection) during the index operation. The decision will be influenced by factors such as the stage of the LC when the suspicion arises, the degree of suspicion and the local expertise available at the time of surgery. If it is safe to stop and properly assess and stage the patient this has the best potential outcomes.

Prior to definitive surgery staging is performed with multi detector computerized tomography (CT) chest abdomen and pelvis, which has an overall accuracy of between 71% and 93% [35–37]. Multiphase imaging, particularly the portal venous phase (65–75 s after intravenous contrast injection) delineates the enhancement patterns [38, 39]. Either a heterogeneously enhancing single thick layer, or a strongly enhancing thick inner layer (>2.6 mm) accompanied by a weakly enhancing/non enhancing thin outer layer (<3.4 mm) are features on CT associated with gall bladder cancer [38]. CT has an accuracy of 83.9% in being able to predict the T stage, as well as the local extent of gall bladder cancer, and the addition of multiplanar reconstruction images increases the accuracy [39].

A limitation of CT is in detecting vascular and biliary invasion. The extent of invasion can be assessed by MRI/MRCP [40]. Diffuse nodular thickening of the gall bladder wall without layering on MRI is associated with gall bladder cancer [41]. There is no definitive evidence of benefit of MRI over CT [42], and hence CT is advocated for the first line investigation of suspected gall bladder cancer and if any features need further evaluation, MRI/MRCP can be performed.

If the staging reveals the disease is confirmed to be T1b, T2 or T3, without evidence of nodal spread beyond the hepatoduodenal ligament or distant metastases, then radical cholecystectomy is recommended.

At times it will not be possible to be certain whether or not a gallbladder cancer is present either prior to laparoscopy (but where it is suspicious), during the index laparoscopy or after staging for a terminated laparoscopy. Attempting to biopsy is potentially hazardous due to the risk of a sampling error (suggesting benign condition) or compromising ultimate outcome if malignancy is confirmed. In this clinical situation of a possible cancer it is preferable to proceed with a radical cholecystectomy (provided patient factors allow) rather than LC as there is proven survival advantage for radical resection over simple cholecystectomy for T1b, T2 and T3 tumours [24, 43]. Furthermore, a benign final diagnosis after a cancer type resection is preferable in most circumstances to leaving transected residual cancer tissue during LC. Conventionally the cancer resection is done by open technique, though there have been recent reports on both the laparoscopic and robotic approaches [44, 45].

Conclusions

Three quarters of patients with IGBC are candidates for revisional surgery [14]. The type of treatment administered depends on the staging of the gallbladder cancer. RO resection (no microscopic residual tumour) is the most important favourable predictive factor for overall survival of gallbladder cancers [46].

A greater awareness of IGBC, and appropriate and timely involvement of specialist HPB/Oncological input is warranted.

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