Surgical management of gallbladder cancer

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Abstract Gallbladder cancer is a very common malignancy in the northern part of India. Surgery is the only potentially curative modality of treatment for this disease. Radical cholecystectomy is the optimal surgical standard for resectable gallbladder cancer. This includes cholecystectomy, liver resection (wedge, segments 4b and 5, or extended right hepatectomy), and regional lymphadenectomy along the hepatoduodenal ligament, behind the duodenum and pancreatic head, common hepatic artery and celiac axis. Controversies regarding extent of liver resection, lymphadenectomy and role of multiorgan resection have been discussed. Incidental gallbladder cancer is often detected on histopathologic examination of the simple cholecystectomy specimen removed for a presumed gallstone disease. Revision surgery should be performed for incidental cancers that invade muscularis propria or beyond (T1b or more). Advanced gallbladder cancer should be treated non-operatively with a palliative intent. Obstructive jaundice in the setting of an advanced gallbladder cancer can be palliated with biliary stenting by endoscopic or transhepatic means. Occasionally, a surgical biliary bypass may be indicated to relieve intractable pruritus in a jaundiced patient with gallbladder cancer. There is no role of a planned R2 resection of advanced gallbladder cancer for the purpose of cytoreduction. Further improvement in the management of gallbladder cancer will need integration of systemic chemotherapy with radical surgery.

Keywords Gallbladder cancer · Radical cholecystectomy · Revision surgery · Segment 3 bypass

Introduction

The cancer of gallbladder has a very diverse geographical variation both worldwide as well as within our country [1]. This disease is extremely common in the northern and eastern parts of India; while being a rarity in the south. Its association with gallstones is quite strong [2] and there have been several epidemiological studies hinting towards the association of certain chemicals and heavy metals in the waters of the major rivers in northern India where the incidence of gallbladder cancer is very high [3]. The association of gallbladder cancer with porcelain gallbladder and chronic typhoid carrier state has also been reported [4, 5]. Despite these studies, the exact aetiological factors to the development of gallbladder cancer remain elusive.

The management of gallbladder cancer is a difficult and often frustrating endeavour. Most often, the disease manifests at an advanced stage when there is no realistic possibility of cure. The symptomatology of gallbladder cancer overlaps significantly with that of gallstone disease, resulting in delayed diagnosis and inappropriate treatment. The only treatment option which has a potential to cure gallbladder cancer is surgery. It is the different approaches towards surgical management of gallbladder cancer that this article focuses on.

Anatomic considerations in context to gallbladder cancer

Gallbladder is a thin-walled organ just below the segments 4b and 5 of the liver with a close proximity to the structures

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in the hepatoduodenal ligament viz. the portal vein, hepatic arteries and bile duct. Unlike other gastrointestinal organs, it has only one muscle layer and hence the tumour gains access to the serosa of the gallbladder when it would be encountering the second muscle layer in other parts of the gastrointestinal tract. Its proximity to the liver and hepatoduodenal ligament means that the cancer of gallbladder will have an early infiltration into these structures, thus making surgical extirpation of the disease much more difficult.

The lymphatic drainage of the gallbladder has been studied carefully using a blue dye technique [6]. The first echelon nodes are the cystic and pericholedochal lymph nodes. From there, the lymphatic connections are made to the nodes along the portal vein, common hepatic artery and posterior to the pancreatic head. Finally, the lymphatic flow reaches the interaortocaval, coeliac and superior mesenteric artery lymph nodes. Importantly, the dye was never seen to ascend towards the hepatic hilum, while the staining of the nodes around portal vein and posterior to pancreatic head was an early event. Some lymphatic connections are present directly between the pericholedochal nodes and the interaortocaval nodes, which explain the difficulty in controlling this disease despite an adequate regional lymphadenectomy.

Diagnostic considerations

The clinical presentation of gallstone disease and gallbladder cancer may be very similar. Because ultrasonography is the diagnostic modality of choice for gallstone disease, this investigation needs to be very carefully performed and interpreted. The features on ultrasonography that may raise suspicion of malignancy are mass in the gallbladder, irregular and thickened gallbladder wall, a polyp >10 mm size, suspicious invasion into the liver, and enlarged pericholedochal nodes [7]. A patient with an ultrasound finding that is suspicious of gallbladder cancer must undergo a contrast-enhanced CT scan of the abdomen. CT scan is helpful in better characterisation of the thickening of gallbladder wall and often demonstrates a mass in the gallbladder or lymph nodes in the hepatoduodenal ligament and peripancreatic region [8]. Endoscopic ultrasound (EUS), as an adjunct to other imaging modalities, may be helpful for the evaluation of the peripancreatic and periportal lymphadenopathy, especially when combined with EUS-directed needle biopsy.

CA 19–9 is a serum marker for gallbladder cancer. A level above 20 U/ml has 79% sensitivity and 79% specificity for the diagnosis of gallbladder cancer [9]. However, in the presence of jaundice, serum levels of CA 19–9 can be elevated even in the absence of malignancy. A carcinoembryonic antigen (CEA) level more than 4 ng/ml is 93% specific for the diagnosis of gallbladder cancer compared to

controls undergoing cholecystectomy for benign conditions, but has a sensitivity of only 50% [9]. These can be used in a suspicious clinical setting, but is not cost-effective as a general screen for all patients undergoing cholecystectomy.

Once a mass suspicious of gallbladder cancer is identified on imaging, the decision to perform a biopsy before definitive exploration is controversial. In general, if the CT scan suggests that the gallbladder cancer is resectable, a preoperative biopsy is not required and a definitive surgical exploration should be performed. In the event of an unresectable gallbladder cancer, image-guided fine needle aspiration cytology (FNAC) should be performed to confirm the malignancy.

Because gallbladder cancer has a remarkable propensity for peritoneal dissemination, laparoscopy should be performed just prior to laparotomy in the same anaesthesia setting to exclude patients with peritoneal seedings from an unnecessary laparotomy. Laparoscopy combined with laparoscopic ultrasonography (LUS) may be quite accurate for the assessment of vascular invasion in the hepatoduodenal ligament, regional lymphadenopathy, and extent of liver invasion. However, the experience with LUS is still evolving and it has not yet found a place in routine surgical repertoire for gallbladder cancer.

Operability in gallbladder cancer

Operability in gallbladder cancer is a subjective decision based on several factors. While non-contiguous liver lesions, ascites, peritoneal nodules and retroperitoneal lymphadenopathy represent metastatic disease and confer inoperability, there are other issues on which the decision is not as simple.

The presence of jaundice in gallbladder cancer is a common occurrence and may be due to extension of disease into the lumen of common bile duct, engulfment or invasion of the bile duct by the gallbladder cancer, pressure or invasion of the bile duct by lymph nodes in the hepatoduodenal ligament, or the presence of associated stone in the bile duct. Transluminal extension of cancer into the bile duct can be taken care of surgically by excision of the extrahepatic bile duct, and the associated stones in the bile duct can be dealt with by endoscopic means or by removing them at the time of definitive surgical exploration. However, these causes of jaundice are rather uncommon. In a vast majority of patients of gallbladder cancer with jaundice, the cause is either invasion/engulfment of the porta hepatis by the primary tumour or by nodes of the hepatoduodenal ligament. These situations are rarely, if at all, resectable.

The extent of liver invasion needs careful assessment. For gallbladder cancer with minimal invasion into the liver, wedge resection of the liver in the gallbladder bed can be performed without much difficulty. Some surgeons advocate

anatomic resection of the segments 4b and 5 of the liver. Both the approaches are reasonable as long as a tumour-free margin in the liver parenchyma is obtained. For a more extensive liver invasion, major hepatectomy may be required, which would often mean an extended right hepatectomy. The decision to perform extended liver resections for a disease that is already locoregionally advanced requires careful judgement, but may be reasonable in an otherwise healthy individual if an R0 resection is obtainable.

The extent of nodal disease is also an important concern. Lymph nodes in the hepatoduodenal ligament can be dissected satisfactorily if they are not infiltrating vascular structures. However, enlarged nodes behind the head of the pancreas or behind the duodenum pose a challenge to the surgical decision. While smaller non-infiltrative nodes can be dissected well by good Kocherization and removal of all the fatty tissue and nodes in the retropancreatic and retroduodenal regions, larger and infiltrative nodes cannot be satisfactorily removed without the addition of pancreatoduodenectomy. Addition of pancreatoduodenectomy to an already major surgical procedure of radical cholecystectomy needs careful judgement and balancing act between the morbidity and mortality of such an endeavour and the possible survival benefit in the presence of gross regional lymphadenopathy.

Surgery for operable gallbladder cancer

Once the gallbladder cancer is found to be operable on preoperative imaging, the patient should be prepared for surgery if there are no overriding medical comorbidities. Staging laparoscopy should generally precede laparotomy. Radical cholecystectomy is the standard and should include cholecystectomy, resection of liver in the gallbladder bed, and regional lymphadenectomy [10]. This surgery has also been referred to as extended cholecystectomy. The controversies in radical cholecystectomy include the extent of liver resection, need for routine bile duct excision, the extent of lymphadenectomy, and the role of multiorgan resection.

The primary aim of liver resection is to achieve tumour-free margins in the liver parenchyma. It can be achieved by performing a wedge resection of the liver in the gallbladder bed, or a formal resection of segments 4b and 5 of the liver, or by extended right hepatectomy [11]. Proponents of a more extensive liver resection believe that this takes care of the potential spread of the cancer through the portal circulation and by the lymphatics. However, non-contiguous lesions in the liver caused by spread through portal circulation are generally incurable. Lymphatic mapping of the gallbladder has shown that the lymphatics do not ascend towards the hepatic hilum. A more pragmatic approach is to tailor the extent of hepatectomy to the degree of liver invasion. A minimal liver invasion requires a wedge resection or a formal

resection of segments 4b and 5, while a more extensive invasion might need an extended hepatectomy if R0 resection can be achieved.

After removing the gallbladder, the cystic duct margin should be inspected and subjected to frozen section, especially if the primary tumour is located in the neck of the gallbladder. If the cystic duct margin is close or positive for tumour, there should be no hesitation in resecting the bile duct and performing a bilioenteric anastomosis. There are surgeons who advocate routine excision of extrahepatic bile duct to facilitate a better lymphadenectomy along the hepatoduodenal ligament [12]. Most surgeons would not routinely resect the bile duct unless it is involved directly by the primary tumour or by a pericholedochal node [13].

The extent of lymphadenectomy is more or less standardised [14]. Lymph nodes in the hepatoduodenal ligament, that include periportal, pericholedochal and hepatic artery nodes, should be routinely dissected. In addition, the lymph nodes behind the pancreatic head and the duodenum, and those along the common hepatic artery and the coeliac axis should also be dissected. There are advocates of more extended lymphadenectomy that would include para-aortic and superior mesenteric nodes.

Multiorgan resection is generally not advocated for gallbladder cancer, but may be required for an occasional patient who has infiltrating nodes in the retroduodenal/retropancreatic region, or has disease that involves adjacent organs like duodenum or colon. Multiorgan resection can be only be justified if an R0 resection can be achieved and provided the patient is in a good general health in order to tolerate such an extensive procedure. Indeed, there are reports from Japan about hepatopancreato-duodenectomy for gallbladder cancer with reasonable outcome [15].

There would be occasions when the surgeon has a suspicion of malignancy while performing laparoscopic cholecystectomy for gallstone disease. In such a situation, laparoscopy should be abandoned and an open cholecystectomy performed. The gallbladder should be subjected to frozen section analysis and a full procedure of radical cholecystectomy should be performed if the frozen section report shows cancer.

Revision surgery for incidental gallbladder cancer

Since there is a considerable overlap between the symptomatology of gallstone disease and gallbladder cancer, gallstones coexist with cancer in a large majority of patients with gallbladder cancer, and ultrasonography may not be sensitive enough for the diagnosis of gallbladder cancer, there are occasions wherein carcinoma is diagnosed on histopathologic examination of the gallbladder removed for gallstone disease. This entity is referred to as an incidental gallbladder cancer. Much

controversy exists regarding the further management of such incidental carcinomas.

The gallbladder contains only one muscle layer and it lacks serosa on the surface that is in contact with the liver. While performing cholecystectomy for gallstone disease, whether laparoscopic or open, the surgeon removes the gallbladder from liver through the plane of the perimuscular connective tissue. If the incidental cancer has breached into the muscularis layer, the possibility of residual disease in its bed after a simple cholecystectomy would be significant. Needless to add, this possibility would increase if there has been an inadvertent perforation of the gallbladder while removing it from the liver, an occurrence that is not uncommon. It is also important to understand that the cancer would have access to lymphatics once it breaches the mucosa, and the chances of lymph node metastasis would increase with the increasing depth of invasion into the wall of the gallbladder.

If the gallbladder cancer is limited only to the mucosa (Tis) or submucosa (T1a), a simple cholecystectomy is curative [16, 17]. In these situations, if the pathologic staging is accurate and the cystic duct margin is negative for tumour, no further treatment is needed. For patients with incidental gallbladder cancer that invades the muscularis (T1b) or beyond, the 5-year survival following simple cholecystectomy is 20–40.5% [17, 18]. These patients need revision surgery [19] which would include wedge resection of the liver in the gallbladder bed, resection of the remnant cystic duct, and regional lymphadenectomy as discussed in the previous section. If the cystic duct margin is positive for tumour, resection of the bile duct and bilioenteric anastomosis is indicated. For patients who have undergone laparoscopic cholecystectomy, resection of the port sites is also recommended because of the high propensity of port site seeding by gallbladder cancer. While the port sites are clearly identifiable on the skin, the sites of entry into the peritoneum and the exact course of penetration of the ports may not be identifiable accurately. The chances of seeding are the maximum on the peritoneal aspect of the laparoscopic port entry and thus, the benefit of routine port site resections is uncertain. The same controversies about the extent of liver resection and the need of routine bile duct resection exist in the patients with incidental gallbladder cancer as well. The extent of surgery notwithstanding, it has been shown that revision surgery leads to improvement in survival for tumours that are T2 or more [20], and this may also be true for T1b tumours.

Palliative surgery for advanced gallbladder cancer

Unfortunately, gallbladder cancer often presents at an advanced stage when there is no realistic possibility of cure. These patients are offered palliative treatment in the form of

best supportive care or palliative chemotherapy. If the patient is jaundiced and has debilitating pruritus, biliary stenting may be performed through endoscopic or transhepatic means. Endoscopic biliary stenting may not be feasible in many occasions because the site of biliary obstruction in advanced gallbladder cancer is usually high; at or near the confluence. Stenting by transhepatic means requires expertise in interventional radiology. Such expertise and facilities may not be widely available, especially in areas of highest incidence in India.

Palliative biliary bypass by surgical means may occasionally be indicated in such patients of gallbladder cancer with obstructive jaundice when either biliary stenting fails or expertise in interventional radiology is not available. As the obstruction is almost always at or near the biliary confluence, segment 3 bypass should be performed in these cases. In an occasional patient whose jaundice is due to retroduodenal/retropancreatic node and the primary tumour does not invade the porta hepatis, a hepaticojejunostomy may be performed.

Segment 3 bypass is an uncommonly performed procedure and has been largely given up with the advances in the endoscopic and interventional radiology techniques that permit a safer placement of a biliary stent and relief of jaundice. However, faced with a large number of patients of gallbladder cancer with jaundice and with the lack of interventional radiology facilities, this procedure has been started again at our centre by the author of this manuscript. In an unpublished series of 18 patients who underwent segment 3 bypass for advanced gallbladder cancer, there was one postoperative death (because of myocardial infarction on postoperative day 2) and there was no anastomotic leak. All patients reported relief from pruritus even when the biochemical reduction in bilirubin was not complete in most instances.

There has been an unnecessary controversy regarding palliative cholecystectomy with an aim of reducing the tumour burden so that chemotherapy can be more effective. Performing a planned R2 resection for gallbladder cancer is unjustified as the patient derives no benefit from the procedure and is subject to unnecessary surgery with its attendant morbidity and potential mortality.

Future directions in the surgical management of gallbladder cancer

In spite of the developments in surgical techniques, the survival results of gallbladder cancer still remain far below desired. Chemotherapy is only modestly effective, gemcitabine alone or in combination with cisplatin or oxaliplatin being the most promising. The future improvements in the results of gallbladder cancer would depend on the rational combination of surgery and chemotherapy. Adjuvant and neoadjuvant approaches need to be studied systematically.

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