

Surgery for gallbladder cancer: The need to generate greater evidence

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Abstract

The outcomes for gallbladder cancer remain largely dismal to this day. Overall, the low incidence of gallbladder cancer around the world coupled with an even lower number of patients amenable to surgery at the time of presentation, has precluded the generation of evidence-based guidelines for the management of this cancer. However, while the incidence of the cancer may be decreasing in some parts of the world, in other countries such as India, Japan and Chile, gallbladder cancer continues to affect a sizeable population of patients. As such, there is a growing need to define what constitutes an adequate surgery for each stage of this cancer, based on sound evidence. This editorial provides a broad overview of the existing problems in the management of gallbladder cancer and appeals for multi-institutional studies aimed at answering some of the pertinent questions on the surgical management of gallbladder cancer.

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INTRODUCTION

It is indeed despairing to read articles on gallbladder cancer outcomes which always begin with the reference to the disease as one that is associated with a dismal prognosis. Surgery remains the only treatment modality associated with a benefit in terms of survival^[1] in gallbladder cancer. However, what is most disconcerting is the lack of consensus across the world on what constitutes an optimal operation for a given stage of the disease. Many of the surgical concepts in gallbladder cancer are based on what “we think” as appropriate. The confusion is aptly summed up by the paper by Sasaki *et al*^[1] in which 16 different resections had been performed. The cause for all this uncertainty stems from the fact that this disease is relatively uncommon around the world and so hardly any (if at all) of the approaches have been evaluated in an evidence-based manner. Another confounding factor is the difference in the etiology and pathogenesis of the disease in Japan (from where most of the reported data on surgical management of gallbladder cancer arises) and the rest of the world^[2]. This brings us to the question of whether we can draw conclusions from the existing literature that can aid us in deciding the correct surgery.

CURRENT SURGICAL PRACTICE

T1 stage

Most surgeons would agree that for a tumor that is T1a by the TNM classification^[3], a simple cholecystectomy constitutes an adequate surgery. However, the view on T1b tumors is not so clear. While some authors have suggested that a simple cholecystectomy is sufficient in such patients^[4,5], we^[6] and others^[7], have found evidence of lymph node metastases in these patients as well as disease in the gallbladder fossa (even up to 35%)^[5,6]. This seems to indicate that performing a lymphadenectomy with excision of at least a wedge of liver tissue from segments 4b and 5 seems to be prudent^[8], the benefit of which needs to be studied in prospective randomized studies.

T2-4

In the case of tumors that are T2-4, the basic principles of resection include a cholecystectomy with an *en bloc* resection of the liver, with a lymphadenectomy with or without a radical resection of the bile duct^[7]. The extent of liver tissue to be resected continues to be a matter of conjecture. Some surgeons routinely prescribe major hepatic resections for all stages of gallbladder cancer^[9-11]. However, there is growing evidence that major hepatic resections are associated with an increased morbidity (intra-abdominal abscesses, bilomas, hepatic failure) and even mortality^[11-13]. Even here, there is increasing evidence that major resections may be devoid of any survival benefit^[9,14,15] as compared to 2-3 cm wedge resections of segment IVb and V.

ROLE OF LYMPHADENECTOMY

In most solid organ cancers, including gastric and colorectal cancers, lymphadenectomy provides important staging information and it may also be associated with a reduction in local recurrence. In gallbladder cancers, while most surgeons perform a standard regional lymphadenectomy (which includes lymph nodes around the cystic duct, pericholedochal and hepatoduodenal ligaments), some surgeons recommend an extended resection to include retroportal, posterosuperior pancreaticoduodenal, posteroinferior pancreaticoduodenal, common hepatic artery, celiac, superior mesenteric and interaorticocaval lymph nodes for tumors that are stage III and IV^[16]. However, the benefit of such an exercise in improving overall survival remains contentious^[17,18]. In addition, attempts should perhaps be made to define a minimum number of lymph nodes (from specific locations) necessary for optimal staging (and perhaps prognostication) of gall bladder cancer.

EXTRAHEPATIC BILE DUCT RESECTION

Japanese surgeons have long since recommended the routine excision of the extra-hepatic bile duct in all stages of gallbladder cancer^[19-21]. The rationale behind

this is that in the early stages of the disease, excision of the bile duct would aid clearance of lymph nodes and occult cancer cells along the hepatoduodenal ligament and in the connective tissue^[22]. In the advanced stages, it was intended to address the issue of perineural invasion^[23]. However, while some Japanese surgeons have demonstrated a benefit in terms of overall survival^[24-26], others have failed to do so^[27-29]. Moreover, numerous studies have highlighted the increased morbidity associated with routine excision of the duct^[27,28,30]. However, despite all this controversy, there do exist specific indications where the extrahepatic duct may have to be excised and these include a positive cystic duct margin, presence of an anomalous bile duct junction, and synchronous malignancy in the extrahepatic bile duct, as well as to aid lymph nodal clearance when there are large lymph nodes, the clearance of which may be associated with a risk of devascularizing the common bile duct.

PORT-SITE METASTASES

With the increasing use of laparoscopic cholecystectomy, there will always be a risk of port-site metastases. Again the management of port-site metastases in patients who are undergoing radical resection for incidental gallbladder cancers seems to be contentious. While, Giuliani *et al.*^[31] recommended routine "complete" excision of the port sites, surgically this may not always be feasible. More importantly, there is no evidence to date to indicate that routine excision of the port sites improves overall survival.

PATIENTS WITH METASTATIC DISEASE

In patients with stage IV disease, there remain proponents of radical surgery^[25,32,33] even in stage IV disease. However, prior to interpreting these results it must be understood that patients with stage IVa and even b need not have distant metastases. Thus the survival advantage that has been demonstrated^[32,33] is primarily in those patients without liver, peritoneal or distant metastases. More robust data is needed to determine whether there exists a survival benefit of radical resections in these patients or, for that matter, even in patients with liver metastases (anecdotal reports exist on the benefit of radical surgery in these patients).

FUTURE PERSPECTIVES

With a reported decline in the incidence of gallbladder cancer (based on the surrogate marker of gallbladder cancer mortality) in the United States, Australasia and most parts of Europe^[34], it appears that the drive to generate more evidence on the appropriate surgery for the cancer must come from countries with a higher incidence of the disease.

Pertinent aspects that need to be answered in the management of gallbladder cancer include: (1) consensus definitions of the various surgeries to be performed for

gallbladder cancer. There has been a considerable overlap and interchangeable use of terms when defining the surgery performed in gallbladder cancer including extended cholecystectomy and radical cholecystectomy^[35]; (2) the role of radical cholecystectomy in T1b disease; (3) the role of extrahepatic bile duct resection in the various stages of the disease; (4) the extent of liver/gallbladder bed to be resected for each stage of the disease; (5) the extent of lymphadenectomy for the different stages of the disease. The latter aspects can probably be best answered by randomized controlled trials which would need a large number of patients to be enrolled in multicenter studies. Such a task would require a large collaborative effort from institutions in high incidence areas around the world.

CONCLUSION

We should accept the fact that gallbladder cancer is a disease with low numbers of patients amenable to surgery. Thus, instead of retrospectively analyzing individual institutional data, high volume institutions with the necessary expertise for treating gallbladder cancer should collaborate with a view to generating strong evidence to support the different surgical strategies - a move that may provide us with the evidence-based surgical guidelines we are looking for to better enable us to tackle this dreadful disease.

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