

Gallbladder Cancer

What Is an Aggressive Approach?

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In the accompanying article by Dixon et al,¹ the hepatobiliary surgery group from the University of Toronto documents a recent improvement in survival in 99 patients with gallbladder cancer. They attribute the increase in 5-year survival from 7% to 35% ($P < 0.03$) to a more aggressive surgical approach. In comparing two 6-year time periods, the only significant differences ($P < 0.04$) in the patients or their management was an increase in liver (17% versus 45%) and biliary tree (9% versus 30%) resection. These results were achieved with a very acceptable operative mortality (2%) and morbidity rate (49%) among the 51 patients who were explored. In a multivariate analysis, the only factors that predicted long-term outcome ($P < 0.01$) were an R0 resection (HR = 0.28) and preoperative weight loss (HR = 2.54).

A very interesting observation by Dixon et al¹ was that the diagnosis prior to intervention was wrong in 62% of their patients. In 50% of the patients, the initial diagnosis was a benign biliary disorder such as biliary colic (24%), acute cholecystitis (12%), or choledocholithiasis (5%). In another 12% of patients, the gallbladder cancer was confused with a perihilar cholangiocarcinoma. As a result, 31% of the patients underwent a cholecystectomy prior to referral, and of the 51 patients who were explored, 50% had a biliary stent placed prior to surgery. These observations document that gallbladder cancer is difficult to diagnose and that treatment at a referral center is frequently complicated by prior interventions.

Dixon et al¹ achieved their excellent results with the infrequent use (5%) of staging laparoscopy, an aggressive approach to liver (45%) and bile duct (30%) resection, a modest portal lymph node dissection, rare (2%) pancreatoduodenectomy, and the occasional use of primarily palliative chemotherapy (17%) and radiation therapy (5%). While most hepatobiliary surgeons agree with the philosophic concept of an “aggressive approach,” considerable controversy exists with respect to the most appropriate pre-, intra-, and postoperative management. Thus, the remaining question in the management of patients with gallbladder cancer is exactly what constitutes an “aggressive approach”?

Ongoing advances in computed tomography and magnetic resonance imaging have helped with preoperative staging and the decision to explore the patient.² The presence of major vascular encasement or metastases should lead to a nonoperative approach. However, approximately two thirds of patients with T-3 and 80% of patients with T-4 gallbladder cancers will have liver and/or peritoneal metastases.³ Thus, the yield of staging laparoscopy is very high in patients with larger gallbladder cancers, and frequent employment of this procedure will often establish a tissue diagnosis and avoid an unnecessary operation.

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Over the past decade, the importance of adding a liver resection to achieve negative margins in patients with a biliary malignancy has been appreciated by most hepatobiliary surgeons.^{1–5} The extent of this resection in patients with gallbladder cancer will vary with the tumor stage. The proposal by Dixon et al¹ to perform an “extended cholecystectomy” (wedge resection of the gallbladder bed) for T2 lesions and resection of segments IVb and V, a right hemihepatectomy or an extended right hepatectomy for more advanced tumors is consistent with most recent recommendations. Thus, the advantage of adding a liver resection and the extent of the liver resection has become a relatively standard part of an “aggressive approach.”

In comparison, the threshold for performing extrahepatic bile duct resection, the extent of lymph node dissection, and the role of pancreatoduodenectomy remain more controversial. Dixon et al¹ resected the extrahepatic bile duct in 66% of their recent 29 patients undergoing a “curative resection.” They recommend extrahepatic bile duct resection in (a) patients presenting with obstructive jaundice and (b) nonobstructive tumors located primarily in Hartmann’s pouch, the gallbladder neck or the cystic duct. However, a recent report from Chiba, Japan, demonstrated histologic invasion of the hepatoduodenal ligament in 55% of 44 patients without preoperative obstructive jaundice.⁶ Thus, resection of the extrahepatic bile ducts in nonjaundiced patients with more advanced tumors should probably become a standard part of an “aggressive approach.”

The lymphatic drainage from the gallbladder extends both along the hepatic artery toward the celiac axis as well as behind the head of the pancreas. Dixon et al¹ describe “a complete portal lymph node dissection, with thorough skeletonization of the portal structures, down to and including the suprapyloric lymph node overlying the hepatic–gastroduodenal artery junction.” Although “complete,” this degree of lymph node dissection is relatively modest compared with that employed by some Japanese groups.⁷ To date, no randomized data are available to answer the question regarding the degree of lymph node dissection resulting in the best prognosis in gallbladder cancer. If randomized data from pancreatic cancer are transferable, a more modest lymph node dissection, as employed by the Toronto group, would still be considered an “aggressive approach.”

Some gallbladder cancers, especially those originating in the fundus, may invade the duodenum without extensive liver involvement. In these rare patients, a pancreatoduodenectomy may be required to achieve a Ro resection. Dixon et al¹ performed a pancreatoduodenectomy in only 1 of 29 (3%) recent curative resections. In comparison, other groups, especially from Japan, have had a much lower threshold to combine a pancreatoduodenectomy with a hepatectomy.⁸ In reviewing multiple smaller series of combined resections over the past decade, the hospital mortality for this extensive procedure remains in the 10% to 15% range. In comparison, the hospital mortality for

pancreatoduodenectomy should be less than 2% and for major hepatectomy, even in jaundiced patients, should be less than 5%. Therefore, the advisability of combining a major liver and pancreatic resection must be questioned, whereas combination of a wedge resection of the gallbladder bed with a pancreatoduodenectomy in the occasional patient with a gallbladder cancer may be appropriately “aggressive.”

Finally, the role of adjuvant chemotherapy and radiation therapy in patients with biliary malignancies remains a matter of debate. Dixon et al¹ selectively employed these therapies for palliation and used adjuvant chemotherapy in only 3 patients. Unfortunately, no randomized data are available, although a number of recent retrospective reports suggest that chemoradiation with 5-FU or gemcitabine as a radiosensitizer may improve survival.² A recent worldwide survey of specialized centers suggests that adjuvant chemoradiation is currently being employed most often in the Americas (70%) and the Asian-Pacific region (55%) and to a lesser degree in Europe (30%). Thus, no consensus exists regarding the role of chemoradiation, but many experts believe that adjuvant chemoradiation is part of an “aggressive approach.”

In summary, hepatobiliary surgeons generally agree that an “aggressive approach” is warranted for patients with gallbladder cancer. However, considerable controversy exists regarding what is meant by an “aggressive approach.” Advances in radiologic imaging and the liberal use of staging laparoscopy in more advanced gallbladder cancers have led to better patient selection for exploration and a higher percentage of curative resections. The performance of a minor or a major liver resection to achieve an Ro resection has become accepted, and a lower threshold to resect the extrahepatic bile ducts is probably warranted. Ideally, multi-institutional randomized trials will be performed to answer the outstanding questions regarding the extent of lymph node resection and the role of adjuvant chemoradiation.

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