

Common Controversies in the Management of Gallbladder Cancer

Presented by Chandrakanth Are, MBBS

Abstract

Gallbladder cancer is a rare and lethal malignancy. Most patients are best served at high-volume centers of excellence, where they are likely to receive evidence-based care derived from a multidisciplinary approach. Surgical resection is recommended for early-stage disease, whereas if the disease is unresectable, the treatment options include biliary drainage, gemcitabine-based combination chemotherapy, fluoropyrimidine chemoradiation, clinical trial enrollment, or best supportive care. While treatment by T-stage is straightforward in many cases, the debate regarding simple versus radical cholecystectomy is still active for patients with T1b disease. Other controversies exist over the necessity of resecting the bile duct and port sites, the extent of lymph node dissection and hepatic resections, and the value of resection for patients with jaundice. (*J Natl Compr Canc Netw* 2014;12:833–835)

Rare in the Western world, gallbladder cancer is a lethal cancer more commonly seen in Eastern countries and some countries in South America. Surgery has the potential to cure most cases of early-stage disease and prolong survival in some advanced cases, whereas chemotherapy offers less benefit and is limited to fluoropyrimidine- and gemcitabine-based combinations with some recent introductions of targeted therapies, such as erlotinib and bevacizumab.

Most patients are diagnosed when they undergo gallbladder surgery for a presumed benign diagnosis, with the cancer found incidentally on the postoperative

histopathology report. The best option for these, and virtually all, patients is to be referred to a high-volume center of excellence. A second resection is often advised in patients with incidentally detected gallbladder cancer, largely in an effort to eradicate residual disease, which is common and can range from 40% to 70% of patients depending on T stage.

Areas of Controversy

Dr. Chandrakanth Are, Associate Professor of Surgery, Fred & Pamela Buffett Cancer Center at The Nebraska Medical Center, discussed 6 areas of controversy highlighted in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Gallbladder Cancer: treatment in T1b disease, need for bile duct resection, extent of lymph node dissection, resection of port sites, treatment of jaundiced patients, and extent of hepatic resection at the NCCN 19th Annual Conference.

Treatment of T1b Disease

Although there is no controversy regarding the best treatment for carcinoma in situ and T1a (simple cholecystectomy), T2 (radical cholecystectomy), T3 (curative or noncurative, depending on several factors) or T4 diseases (no surgery; treatment with noncurative intent), a debate exists about how to treat patients with T1b disease: with simple or radical cholecystectomy (Table 1). The concern is the high incidence of residual disease (10%) and positive lymph nodes (15%) seen in patients with T1b disease.

“Until a few years ago, we were not advocating radical cholecystectomy in patients with T1b disease, but based on the data, it’s probably what we should be doing,” Dr. Are suggested. “In patients with T1b incidentally detected gallbladder cancer, the current recommendation is to re-resect

Presented by Chandrakanth Are, MBBS, Associate Professor of Surgery, Fred & Pamela Buffett Cancer Center at The Nebraska Medical Center, Omaha, Nebraska.

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Correspondence: Chandrakanth Are, MBBS, Fred & Pamela Buffett Cancer Center at The Nebraska Medical Center, 984030 Nebraska Medical Center, Omaha, NE 68198. E-mail: care@unmc.edu

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Table 1 Treatment Recommendations by Stage for Gallbladder Cancer

Stage	T	N	M	Treatment
0	Tis	N0	M0	Curative C
I	T1	N0	M0	Curative C+/- HR/LN/CBDR
II	T2	N0	M0	Curative C+ HR/LN/CBDR
IIIA	T3	N0	M0	? Curative C+ HR/LN/CBDR
IIIB	T1-3	N1	M0	? Curative C+ HR/LN/CBDR
IVA	T4	N0-N1	M0	? Noncurative
IVB	Any T	N2	M0	Noncurative
	Any T	Any N	M1	Noncurative

Abbreviations: ?, resection for some patients, but most will be unresectable; C, cholecystectomy; C+/-, simple or radical cholecystectomy; CBDR, common bile duct resection with or without Roux-en-Y hepaticojejunostomy; HR, hepatic resection; LN, lymphadenectomy.

and perform a radical cholecystectomy if they can tolerate the surgery and anesthesia. Studies have shown that many patients even with T2 disease do not undergo repeat resection. For this reason and because of the rarity of the disease and the lack of expertise in treating it, these patients should be referred to high-volume centers of excellence.”

Resection of the Bile Duct

Historically, the common bile duct was routinely resected, based on the assumption that it would enhance the completeness of lymphadenectomy. “That school of thought changed when studies showed that this practice increased morbidity, but did not consistently improve lymph node retrieval or provide a survival benefit,” he indicated.

The current recommendation is selective resection in patients with a positive cystic duct margin ($\approx 40\%$ will have common bile duct involvement), and in patients for whom extensive dissection has devascularized the bile duct.

Extent of Lymphadenectomy

The minimum number of lymph nodes that should be removed is still unclear. In a SEER analysis of 3209 patients, 2507 of whom had data available regarding lymph nodes, 68.0% were found to have no nodes removed, 28.0% had 1 to 4 removed, and only 3.6% had 5 or more removed.¹ Survival was correlated with number of nodes removed (hazard ratio [HR] for death, 0.55 for 1–4 vs 0; and HR, 0.63 for ≥ 5 vs 1–4). Similar findings were seen in a study from Memorial Sloan-Kettering Cancer Center, which found that an average of 3 nodes were removed and that survival increased for those with

6 or more nodes removed compared with less than 6.²

Guidelines are expected soon from an Americas Hepato-Pancreato-Biliary Association (AHPBA)–sponsored consensus conference on the multidisciplinary treatment of bile duct cancer (held in January 2014). Dr. Are predicted that guidelines regarding the minimum number of lymph nodes to be removed will be included.

Resection of Port Sites

In laparoscopic cholecystectomy, during which the gallbladder is removed through a small incision, a sizeable proportion of patients will develop metastatic disease at the port sites. The question has been whether or not to resect these sites.

A Swedish national study of nearly 12,000 cholecystectomies found that 16% of patients developed metastasis at the port site³; this number was replicated in a more recent study from Memorial Sloan-Kettering Cancer Center (n=113) that found a 19% occurrence among the 69 patients who underwent port-site resection. Port-site disease was noted only in patients with stage T2 and T3 disease.⁴ Port-site metastasis significantly reduced median overall survival from 42 to 17 months; however, when adjusted for T and N stage, survival in R0 patients was not affected by the resection of port sites.

“The current thought is that the presence of port-site metastasis is a surrogate marker for underlying aggressive disease, and your treatment will not alter the outcome of the disease in the long term,” Dr. Are said. “The recommendation, therefore, is not to resect the port sites.”

Resection in Patients With Jaundice

Conventional thinking has been that jaundice is a poor prognostic sign and, therefore, is an absolute contraindication for resection. Several studies have shown that patients with jaundice have significantly worse survival than patients without.^{5,6} These studies, however, were from the United States and Western Europe, where the incidence of gallbladder cancer is very low. Studies from high-incidence areas, such as Northern India and Japan, have shown improved survival when jaundiced patients undergo resection (overall survival, 50% at 2 years⁷; 23% at 5 years⁸).

Current consensus states that jaundice is a relative, not an absolute, contraindication for surgery. Patients with the appropriate T-stage disease with no contraindications who are fit enough for surgery and anesthesia should be considered for resection at high-volume centers after careful screening by a multidisciplinary approach.

Extent of Hepatic Resection

Standard of care for radical cholecystectomy is to resect segments 4b and 5 of the liver. Whereas some studies have suggested that more extensive resection is associated with improved survival, others have not. The current recommendation is that resection of segments 4b and 5 are adequate, except in selected cases where more extensive surgery will help obtain negative margins.

Future of Gallbladder Cancer Treatment

Dr. Are suggested that improvements in survival for patients with gallbladder cancer will only occur when the biology of the disease is better understood. “We

need to know more about risk factors and factors that contribute to geographic variation, and about what causes patients to progress from harboring benign disease to cancer,” he said. “When we have this information, we can diagnose patients at an earlier stage of disease and influence long-term survival.” Advancements in chemotherapy will be crucial to improving the survival for patients diagnosed with this lethal malignancy. Finally, these patients will benefit from referral to high-volume centers with expertise and the uniform application of a multidisciplinary approach.

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