Diagnostic and Management Issues in Gallbladder Carcinoma

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This paper by Abi-Rached and Neugut provides an overview of the diagnosis and treatment of gallbladder carcinoma, a rare, yet frustratingly difficult disease to manage [1]. Overall, we agree with the risk factors described in this review. We would add that, in addition to chronic cholecystitis, porcelain gallbladder, and retained gallbladder (secondary to cholecystostomy), cholecysto-enteric fistulas have also been associated with a higher incidence of gallbladder carcinoma [2,3]. Patients with ulcerative colitis are known to be at higher risk for cholangiocarcinoma, and there is also some evidence that these patients have an increased risk of gallbladder cancer.

Benign adenomas of the gallbladder have been described as incurring a slightly increased risk, but this evidence is not very convincing. In a recent paper from Chile, where a high incidence of benign and malignant gallbladder disease has been noted, a definite association between metaplasia in the specimen and the age of the patient was reported [4]. In addition, severe hyperplasia is associated with higher incidences of dysplasia and carcinoma in situ, inferring a progression from hyperplasia and dysplasia to carcinoma in situ.

Presentation

As mentioned in the Abi-Rached/Neugut review, patients with gallbladder cancer often present with classic symptoms of benign gallbladder disease, with persistent, gnawing pain in the right upper quadrant as the disease progresses. In one large series, the average duration of symptoms prior to presentation was 3 months [3]. The presence of jaundice is an indicator of advanced, unresectable disease. Ultrasound is the most sensitive and informative initial test, as most patients being evaluated have benign gallbladder disease; however, CT provides better anatomic detail in evaluating the liver and porta hepatis for adenopathy in patients with advanced disease. Unfortunately, current imaging techniques too often fail to detect small lesions such as peritoneal implants.

The role of surgery in the treatment of gallbladder carcinoma continues to be reevaluated in the surgical literature. Most authors agree that simple cholecystectomy is adequate therapy when tumors are confined to the mucosa or barely penetrate the muscularis propria layers [2]. Survival in this select group ranges from 60% to 90%, and in several series approaches 100%. Unfortunately, only 5% to 10% of cases present with asymptomatic gallbladder cancer and have limited invasion of the gallbladder wall.

Radical surgery has been shown to improve survival in selected patients when disease extends beyond the muscularis and into the serosa (or into the liver). In a recent German series of 113 patients, the median survival was 14 months after curative resection and 5.8 months after palliative resection, compared with 3.6 months after exploration alone. In another series, from the Mayo Clinic, that included 111 patients, the median survival after radical cholecystectomy was 3.6 years vs 8 years after simple cholecystectomy. In this series, survival was related to stage, ranging from 100% in patients with stage I (mucosal) to 25% in patients with stages III and IV disease (muscularis/serosal invasion). In several series, patients with disease limited to invasion of the muscularis/serosa, survival was markedly better with radical cholecystectomy (90%) than with simple cholecystectomy (41%) [6]. Although survival in patients with stage III (into serosa) or stage IV (nodal disease) is poor in Western series of patients (less than 10%), survival in Japanese series is reported to be 20% [6]. This may
represent major genetic differences, as well as possible therapeutic differences. In a large Japanese series that included 2,567 patients, the 5-year survival for patients with stage III and stage IV disease was 20% [6]. As expected, survival was significantly lower in patients with transmural tumor infiltration or nodal metastasis than in those with cancer confined to the gallbladder wall.

**Achieving Local Control**
The goal of radical cholecystectomy is to provide adequate control of local disease. Gallbladder carcinomas spread most commonly by direct hepatic extension through the periportal lymphatics. The lymphatics drain into the cystic node and the common duct nodes, into the pancreatic, duodenal, celiac axis, and para-aortic nodes. Therefore, an adequate resection requires dissection of nodes along the cystic duct, portal vein, and common duct, and peripancreatic area. In addition, most recommend resection of a 3 cm to 4 cm margin of normal hepatic parenchyma underlying the gallbladder bed (Segment IVB, V), removing the specimen en bloc from the peritoneal cavity. The margins are marked with radiopaque clips, should external beam radiotherapy be considered postoperatively.

Evaluation of prognostic indicators provides for a more rational approach to reoperation on patients who have undergone cholecystectomy. In a recent study, immunohistochemical staining with a monoclonal antibody against CA 19-9 was used to predict lymph node spread of cancer. In 23 patients with gallbladder cancer, CA 19-9 was present in pathology specimens from all 23 patients. Twelve samples showed staining in the connective tissue stroma adjacent to cancer cells, while the remaining 11 did not show any stromal staining. Lymph node metastasis was found in 75% of the patients with stromal staining, and only 18% of the patients without stromal staining [7,8].

In another study, the role of the c-erb B-2 gene and protein expression and tumor invasiveness were examined in 43 patients with gallbladder carcinoma, using immunohistochemistry and the polymerase chain reaction [9]. Fourteen of the 43 cases showed positive immunoreactivity and c-erb B-2 protein overexpression, although no statistically significant correlation was found with tumor differentiation, invasion, and lymph node metastasis. Further studies are needed to help clinicians identify those patients who would most benefit from radical surgery.

**Preventing Iatrogenic Spread**
Finally, we should mention the potential for iatrogenic dissemination of gallbladder cancer during laparoscopic surgery [5]. Since 1992, 14 cases have been reported in the literature. In one series, ten patients diagnosed with gallbladder cancer via laparoscopy were further explored. In three of the ten, a subsequent radical resection was performed, with curative intent. Four patients had intraperitoneal spread, not present at original laparoscopy, which precluded potentially curative resection. In two of these patients, tumor growth was noted within the laparoscopy tract. The median interval between initial exploration and reexploration was 30 days. These data suggest that laparoscopic surgery should not be undertaken if radiologic or clinical criteria suggest the diagnosis of gallbladder cancer. Furthermore, if this diagnosis is suspected on visual inspection during laparoscopy, the procedure should be abandoned.

In conclusion, in patients who are found to have carcinoma invading mucosa or the muscular coat, cholecystectomy alone should suffice. If there is extension into or through the serosa, a radical cholecystectomy should be done after careful imaging to exclude metastases to the liver or beyond.

**References:**


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