Diagnostic and Management Issues in Gallbladder Carcinoma

Review Article [1] | December 31, 1994
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Carcinoma of the gallbladder is a rare malignancy, with an incidence rate in the United States of 2.2 to 4.4 per 100,000 persons. Its clinical presentation is nonspecific, and the majority of patients have advanced disease at diagnosis.

Introduction

Carcinoma of the gallbladder is an uncommon gastrointestinal malignancy that has a very poor prognosis. Since the original description of this cancer by Maximilian de Stoll in 1777, studies have established a characteristic pattern of late diagnosis and ineffective treatment.

In this article, we review the clinical pathology of the tumor and current results of therapy.

Incidence

Carcinoma of the gallbladder ranks fifth in incidence of gastrointestinal carcinomas and represents about three-fourths of extrahepatic biliary tract carcinomas [1]. Data from the National Cancer Institute's Surveillance, Epidemiology and End-Results (SEER) Program showed that, of a total of 160,238 carcinomas diagnosed from 1973 to 1975, 750 (47%) were gallbladder carcinomas [2]. Piehler and Crichlow, in a 1978 review [3], reported 1,091 instances of gallbladder carcinoma found during 57,170 biliary tract operations during a 15-year period--a prevalence rate of 1.91%. This represented a 35% increase over the 1.41% rate reported by Strauch [4] in 1960. It is difficult to determine whether this increase is real or related to more accurate reporting, however. In the same review by Piehler and Crichlow, results of reports appearing since 1960 documented 303 patients with carcinoma of the gallbladder discovered in 55,543 autopsies--a prevalence rate of .55%. The annual incidence of gallbladder carcinoma in the United States is 2.5 to 4.4 per 100,000 persons [5]. The incidence of this cancer has been estimated to be six times higher in Southwest American Indians than in non-Indian populations.

Carcinoma of the gallbladder is a disease of elderly women, with a female to male ratio of about 3.2 to 1. The mean age at diagnosis, from 29 series, was 65.2 years [3]. When stratified by age, the incidence of gallbladder carcinoma was .3% in those under 50 years of age, 3.8% in those over 50 years old, and 8.8% in those older than 65 years of age [6].

According to the Roswell Park experience, diabetes mellitus is present in 8.5% of patients with gallbladder carcinoma [7]. Reports on the subsequent incidence of a second primary cancer have varied from 5% to 20% [7-9].

Etiology

Although the etiology of gallbladder carcinoma is unknown, several epidemiologic risk factors have been proposed. Of these, cholelithiasis has been most frequently implicated as a possible risk factor.

Cholelithiasis

Cholelithiasis is found in 68% to 98% of patients with gallbladder cancer [7,8]. Interestingly, the risk of gallbladder carcinoma increases directly with gallstone size [10]. On the other hand, numerous autopsy series have reported an incidence of gallbladder carcinoma of only 1% to 3% among all patients with cholelithiasis [11]. Furthermore, in a series of 112 patients with asymptomatic gallstones followed for 10 to 25 years, there was not a single case of carcinoma [12]. Finally, about 25% of gallbladder carcinomas develop without documented cholelithiasis [3,4].

Thus, controversy exists over the interpretation of the association. However, gallstones and gallbladder cancer most likely share a common risk factor rather than a causal relationship.

Gallbladder Inflammation and Calcification
A history of antecedent chronic cholecystitis was present in 40% to 50% of patients with carcinoma of the gallbladder, which led to the incrimination of cholecystitis as an etiologic factor. This association is extremely difficult to evaluate, however. Calcification of the gallbladder itself, the so-called porcelain gallbladder, is a significant risk factor for gallbladder cancer, with an incidence ranging between 12.5% and 61% [13,14]. The risk of cancer in typhoid carriers is six times higher than that in the general population [15].

**Benign Neoplasms**

There is a very small risk, if any, for malignant degeneration of benign tumors of the gallbladder without associated cholelithiasis. Phillips [16] studied 500 papilloma cases and found one case of adenocarcinoma. Christensen and Ishak [17] found 3 of 29 nonpapillary adenomas to contain carcinoma in situ.

**Chemical Carcinogens**

Mancuso and Brennan [18] have reported both a higher incidence and earlier onset of gallbladder cancer in rubber industry workers than in controls. In animal models, chemical carcinogens, especially nitrosamines and methylcholanthrene, have been implicated in the etiology of gallbladder cancer [19].

**Clinical Presentation**

In its early stages, carcinoma of the gallbladder is usually asymptomatic. The lack of specific signs or symptoms prevents detection of this cancer at an early and resectable stage. Moreover, when symptoms do occur, they usually resemble those of benign gallbladder disease.

Common symptoms include abdominal pain, nausea, vomiting, weight loss, and anorexia (Table 1). A changing pattern of the character of the pain is usually described. The median duration of symptoms varies from 1.8 months to 3 years [4,7,8]. Physical findings may include tenderness or a mass in the right upper abdominal quadrant, jaundice, cachexia, fever, and ascites.

**Diagnosis**

Nevin Staging System for Gallbladder Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
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<tbody>
<tr>
<td>I</td>
<td>Tumor involves mucosa only</td>
</tr>
<tr>
<td>II</td>
<td>Tumor involves submucosa and muscularis mucosa</td>
</tr>
<tr>
<td>III</td>
<td>Tumor involves submucosa, muscularis mucosa and muscularis propria</td>
</tr>
<tr>
<td>IV</td>
<td>Tumor extends into the liver or distant spread</td>
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Laboratory findings in patients with gallbladder carcinoma are nonspecific. Liver function abnormality is the most common lab finding in these patients. Serum alkaline phosphatase, direct bilirubin, and serum aspartate aminotransferase levels are elevated in 50% or more of cases. The typical patient is mildly hypoalbuminemic. Only 10% of patients have a hemoglobin level lower than 11 g/dL [20].

Ultrasonography is abnormal in 98% of patients (with findings including cholelithiasis, a thickened gallbladder, a mass in the gallbladder, or some combination) and is diagnostic for cancer in 22% of cases. In other review articles [7,8] none of 146 patients with gallbladder cancer was diagnosed prior to surgical exploration.

**Impact of Advances in Imaging**

To study the effect of recent advances in diagnosis and their impact on survival of patients with gallbladder cancer, Ouchi and colleagues [21] compared two groups of patients: Group I, who underwent resection between 1960 and 1978, and group II, who had surgery between 1979 and 1991. Preoperative diagnosis, including suspected carcinoma, was made in 42% of group I patients and 60% of group II. A definitive preoperative diagnosis of gallbladder carcinoma was made in 8% of group I and 36% of group II. The diagnostic accuracy of ultrasonography and CT scanning in the two groups was 36% and 70%, respectively. In another study, CT was diagnostic in 6 of 12 patients (50%) [20]. Of 157 histologically proven positive nodes in 51 patients with gallbladder carcinoma, 60 (38%) were visualized at CT scanning [22]. In summary, preoperative diagnosis of gallbladder carcinoma is uncommon. Nevertheless, recent advances in biliary tract imaging have increased the diagnostic yield.

**Staging**

The first staging system for gallbladder carcinoma was developed by Nevin and coworkers in 1976 (Table 2) [23]. It is based on the level of tumor invasion. Recently, a TNM system was adopted (Table 3) [24]. Both systems correlate very well with prognosis [20,23,25].

**Pathology And Pattern Of Spread**

Adenocarcinomas account for 85% of all gallbladder cancers; 6.5% of gallbladder malignancies are epidermoid carcinomas and 4.5%, adenoacanthomas. Other histologic types include small (oat) cell carcinomas [26], carcinoid tumors, and anaplastic carcinomas [3]. Adenocarcinoma is further divided into glandular, medullary, scirrhouss, papillary, and colloid types, with incidences of 35.3%, 23.2%, 15.7%, 14.5%, and 11.3%, respectively [1]. Histologic grade is
characterized as well differentiated, moderately differentiated, or poorly differentiated.

### Principal Sites of Metastasis for Gallbladder Cancer

Direct invasion of adjacent organs is the most common feature of disease extension. The major means of spread are lymphatic, vascular, neural, intraperitoneal, and intraductal. Intraductal spread of gallbladder carcinoma is characteristic of the papillary subtype, which probably explains the more favorable prognosis of this type of tumor. In 984 patients from nine series, invasion of the liver and lymph nodes by tumor was noted in 69% and 45% of patients, respectively (Table 4) [3].

### Treatment

#### TABLE 5

**Distribution and Survival for Each Stage (Nevin Stage of Gallbladder Cancer)**

The overall survival of patients with gallbladder carcinoma is poor, with fewer than 5% of patients still alive at 5 years after diagnosis. This poor survival is related to the advanced stage of the disease at presentation. According to the Nevin staging system, 55.5% of patients have stage V disease at presentation (Table 5) [25].

### Surgery

In a small minority of early lesions, surgery offers a possibility of long-term survival. The types of procedures performed on 3,054 patients from 87 series are listed in Table 6 [3].

**Role of radical operations**—To improve survival rates, radical operations have been advocated, especially in Japan, but no solid data exist to justify these procedures. Morrow and associates [29] concluded that use of radical operations in patients with stage I to III disease increased the chance of survival. However, no conclusion could be drawn when simple cholecystectomy was compared to cholecystectomy plus lymphadenectomy and/or liver wedge resection, because the patient numbers were too small. Table 6

**Types of Procedure Performed in 87 Series of Patients With Gallbladder Cancer (N = 3,054)**

Donohue and colleagues from the Mayo Clinic [20] reviewed their experience with resection in 111 patients with gallbladder carcinoma. Of these, 20% underwent a simple cholecystectomy and 16% had potentially curative radical cholecystectomy procedures. Although simple and radical cholecystectomy had comparable 5-year survival rates (33% vs 32%), there was a difference in favor of radical cholecystectomy in patients who had transmural extension or lymph node metastasis. Gagner and associates [25], in their review of radical operations for gallbladder carcinoma in the
United States, sent a multiple-choice questionnaire to 76 surgeons regarding the type of procedure performed. Answers from 43 respondents were analyzed. For mucosal invasion, the majority of surgeons (63%) recommended cholecystectomy alone, and a small group (21%) advocated the addition of node dissection.

There was obvious controversy over the surgical approach for subserosal lesions, as 26% of surgeons advocated cholecystectomy alone; 26%, cholecystectomy with node dissection; and 30%, cholecystectomy with node dissection and wedge resection. For serosal lesions, microscopic or macroscopic liver invasion, and positive nodes, 40% to 49% of respondents recommended a combination of cholecystectomy with node dissection and wedge resection.

Palliative measures were cited as appropriate for patients with metastatic disease by 35% of surgeons. These measures included drainage, chemotherapy, or both. Another 30% of respondents favored no treatment for metastasis.

No uniform pattern of approach emerged from this analysis, in part because no conclusions can be drawn from the present North American literature about the usefulness of radical operations for carcinoma of the gallbladder [25]. Although there have been reports of long survival after radical operations, these isolated reports are unsuitable for statistical analysis.

Finally, Wanebo and Vezeridis [30] in their review of gallbladder cancer, recommended the following: In patients with gallbladder cancer invading the mucosa only or invading into but not through the muscular coat, cholecystectomy should suffice. If there is extension to or through the serosa, a radical cholecystectomy should be recommended, pending the exclusion of metastasis. Patients with extension into the liver are best considered for protocol therapy.

**Radiation Therapy**

Local recurrence is a common cause of death in patients who relapse after cholecystectomy. Local recurrence was present or was a cause of death in 86% of 110 patients who died within 5 years after simple cholecystectomy [31].

Hanna and Rider [32] reported on 51 patients with cancer of the gallbladder, 35 of whom had radiation therapy. Radiation increased the total survival of patients who received curative or palliative treatment.

In a retrospective review, [1] the median survival of patients receiving postoperative radiation was 63 months, as compared with 29 months for patients receiving surgery only. This difference was not statistically significant, however.

Another study, from a French group [33], reported a median survival duration of 8 months in 18 patients with Nevin stage IV or V disease who underwent radiation therapy (4,200 cGy). This survival duration is longer than that in historical controls.

In a prospective study, [34] seven patients received adjuvant radiation therapy. None of them had visible gross tumor after gallbladder removal. Five patients were still alive with no evidence of disease at 5, 9, 11, 31, and 58 months.

Intraoperative radiotherapy has been used in carcinoma of the biliary tract system [35]. Todoroki and associates [36] treated six patients who had unresectable gallbladder carcinoma with a single 2,500- to 3,000-cGy dose of radiation. Mean survival duration was 13 months.

In another report by the same group [37], 17 of 27 patients with stage IV (TNM staging) carcinoma of the gallbladder underwent resection plus intraoperative radiation therapy with or without external radiotherapy. The 3-year cumulative survival rate was 10.1% for resection plus intraoperative radiation therapy, as compared with 0% for resection alone.

In summary, data on radiation therapy for gallbladder carcinoma are sparse. Studies are retrospective, with small numbers of patients included. Although there is a suggestion that adjuvant and palliative radiotherapy may improve survival, these approaches cannot be considered part of standard therapy.

**Chemotherapy**

Because of the low incidence of gallbladder carcinoma, the role of chemotherapy has not been well defined.

The most commonly used chemotherapeutic agents have been fluorouracil, doxorubicin, methotrexate, lomustine (CeeNu), etoposide (VePesid), and cisplatin (Platinol), alone or in combination; all of these agents have had very limited objective responses [7,8]. Although patients who received chemotherapy had better survival rates than patients who did not, no reliable conclusion can be drawn from these reports, [7,8] because any benefit can be attributed to patient selection.
The Eastern Cooperative Oncology Group [38] compared fluorouracil alone to fluorouracil plus streptozotocin (Zanosar) to fluorouracil plus lomustine in patients with advanced disease (stage IV and V). The three treatment regimens had overall response rates of 11%, 12%, and 5%, respectively. There was no evidence that combined therapy improved response or survival rates over fluorouracil alone. In a European Organization for Research and Treatment of Cancer study [39], a 10% overall response rate was observed with mitomycin C.

Intra-arterial infusion of chemotherapeutic agents has been used, with conflicting results. Smith and colleagues [40] treated 11 patients with unresectable cholangiocarcinoma or gallbladder cancer with a hepatic infusion of fluorouracil plus mitomycin (Mutamycin). They reported a response rate of 63%. The patients with gallbladder carcinoma had a median survival duration of 12.5 months, which was better than that seen in historical controls.

Makela and Kairaluoma [41] used superselective intra-arterial chemotherapy with mitomycin in 27 patients with gallbladder cancer. They found no convincing evidence that mitomycin has any significant clinical effect when administered by intra-arterial infusion at 6-week intervals.

Conclusion

The prognosis of gallbladder cancer depends on the stage of the tumor at the time of diagnosis. The overall 5-year survival rate is less than 5% (Table 5) [2]. Improvement in imaging techniques may increase the number of early-stage tumors diagnosed and subsequently improve survival. Prophylactic cholecystectomy has been suggested for patients with gallstones as a preventive measure against the development of gallbladder carcinoma, but it is not cost effective. Prophylactic cholecystectomy may be a consideration for high-risk patients, such as Southwest American Indians, however.

Finally, prospective randomized studies are needed to compare simple cholecystectomy to radical surgery in patients with gallbladder carcinoma and to define the respective roles of external-beam and intraoperative radiation therapy. Also needed are phase II trials testing the efficacy of new chemotherapeutic agents.

References:


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