Surgical Treatment and Outcomes in Carcinoma of the Extrahepatic Bile Ducts

The University of Rochester Experience

Dennis Blom, MD; Seymour I. Schwartz, MD, FACS

Hypothesis: To our knowledge, few individual surgeons and only a handful of institutions have gained a meaningful experience with the treatment of adenocarcinoma of the extrahepatic bile ducts or cholangiocarcinoma. The purpose of this study was to critically evaluate the experience of a single center in the treatment of these tumors.

Design: Retrospective cohort study with a median follow-up of 48 months.

Setting: Department of surgery at a university referral center.


Main Outcome Measures: Prognostic variables, resectability rates, morbidity, and survival.

Results: Thirty-eight male and 39 female patients were studied (median age, 71 years). Twenty-three patients (30%) underwent curative resections, 32 patients (41%) underwent palliative surgery, and 22 patients (29%) received nonoperative therapies. The 30-day perioperative morbidity rate was 18%, and mortality was 6%. Overall median survival was 11 months; 4 months for patients receiving nonoperative therapy; 8 months for patients receiving palliative surgery; and 72 months for curative resection. Five-year survival rates were 23%, 0%, 10%, and 55%, respectively. Curative resection was the only prognostic variable to have a statistically significant effect on survival.

Conclusions: Curative resection could be achieved in approximately one third of patients who had cholangiocarcinoma, and should be the goal of treatment. Survival is significantly improved in those patients who are considered to have resectable tumors and who undergo removal of all gross disease. Palliative surgical treatments also revealed a survival advantage over nonoperative therapies.


ADENOCARCINOMA OF the extrahepatic bile ducts, or cholangiocarcinoma, is a rare malignant neoplasm. In the United States, it is estimated that extrahepatic biliary cancers will represent less than 1% of all new cancers and less than 3% of gastrointestinal cancers in the year 2000. During the same period, approximately 50% of these patients will die of their disease.1 Because of this, few individual surgeons and only a handful of institutions have gained significant experience with these tumors.

Often referred to as Klatskin tumors, after the internist Gerald Klatskin who described 13 cases of sclerosing adenocarcinoma localized to the hepatic duct bifurcation in 1965,2 the first resection of a primary cancer of the hepatic duct bifurcation was reported by Brown and Myers3 in 1954, and in 1957, Altmeier et al4 described proximal bile duct neoplasia as a cause of jaundice. The precise cause of these tumors remains unknown. Cholangiocarcinoma is uncommon in patients younger than 40 years, with most tumors occurring in patients aged between 50 and 70 years. When discovered, they tend to be small, exhibit a slow rate of growth, and rarely metastasize.5 Reported resectability rates, however, vary widely in the literature (10%-90% resectability).4,5,6 Local invasion and proximity of vital structures within the porta hepatitis contribute to the difficulty in achieving complete tumor clearance, and local recurrence is common. For these reasons, cholangiocarcinoma continues to represent a therapeutic dilemma and technical challenge to the surgeon, leading many to adopt a nihilistic approach to the treatment of these tumors.6,7-9
PATIENTS AND METHODS

Medical records of all patients evaluated and treated for adenocarcinoma of the extrahepatic bile ducts at the University of Rochester School of Medicine and Dentistry (Strong Memorial Hospital, Department of Surgery, Rochester, NY) between January 1980 and February 1998 were retrospectively reviewed. Patients without pathologic confirmation of the diagnosis of adenocarcinoma of the extrahepatic bile ducts, or with a diagnosis of carcinoma of the Vater ampulla, carcinoma of the gallbladder, or primary adenocarcinoma of the intrahepatic bile ducts were excluded from this study.

Admission notes, consultations, laboratory reports, radiologic imaging reports, operative reports, and pathology reports, as well as discharge summaries and follow-up records were reviewed. Variables measured at admission included patient demographics, the symptoms of pain and pruritus, jaundice, weight loss, presence of cholangitis, total serum bilirubin (mg/dL), and alkaline phosphatase (U/L). Preoperative diagnostic modalities, tumor location, and type of operation were recorded. Tumor location was categorized into upper, middle, and lower tumors based on the system of Longmire et al.20 The main outcome measures were tumor resectability, the development of complications, and survival. Perioperative morbidity and mortality were defined as any complication or death occurring within 30 days of operation.

Patients were grouped into 1 of 3 categories: tumor unresectable for cure, nonoperative intervention (group 1); tumor unresectable for cure, palliative surgical procedure performed (group 2); and tumor potentially resectable for cure (group 3). A potentially curative procedure was defined by the ability to remove all tumor with negative surgical margins at the initial operation. Palliative procedures consisted of any operation that left residual tumor in situ.

Patient survival was calculated using the Kaplan-Meier method and included all hospital deaths. Survival differences were assessed using the log-rank test. Univariate analysis was accomplished using the χ² test for nominal data and 1-way analysis of variance for comparisons of mean values. A P value less than or equal to .05 was considered to be significant. Statistical analysis was performed using SPSS version 7.5 (Statistical Package for Social Science; SPSS Inc, Chicago, Ill).

The purpose of this study was to critically evaluate the experience of a single tertiary referral center in the treatment of adenocarcinoma of the extrahepatic bile ducts and to determine the prognostic factors, the rate of tumor resectability, morbidity rates, and survival for these patients.

RESULTS

Seventy-seven patients with adenocarcinoma of the extrahepatic bile ducts were studied. There were 39 women and 38 men with a median age of 71 years (range, 38-89 years). Median time to follow-up was 48 months (range, 1-96 months). Patient characteristics and admission findings are listed in Table 1. No significant differences were found between study groups. Five patients (7%) underwent operative procedures without a radiologic workup that consisted of computed tomography scanning of the abdomen and/or biliary imaging using endoscopic retrograde cholangiopancreatography and percutaneous transhepatic cholangiography. Painless jaundice was the admitting complaint in 44% of patients.

The distribution of tumor locations for each of the patient groups is presented in Table 2. Forty-five percent of patients had tumors of the upper third of the extrahepatic biliary system, 38% had tumors of the middle third, 7% had tumors of the lower third, and 10% had diffuse disease. No significant differences were found in tumor location between study groups.

Tumor resectability was determined by the operating surgeon, and based on preoperative imaging studies or findings at celiotomy. Twenty-two patients (29%) were determined preoperatively to have unresectable tumors and underwent nonoperative therapies such as percutaneous transhepatic or endoscopic biliary drainage. Fifty-five patients (71%) underwent an exploratory celiotomy. Of these 55 patients, 32 (58%) had a palliative resection and/or a biliary bypass procedure after it was determined intraoperatively that a complete curative resection could not be safely performed. The remaining 23 patients (42%) underwent a potentially curative resection. In 16 patients, this consisted of the complete resection of the tumor and a Roux-en-Y biliary-enteric reconstruction; 4 patients underwent pancreaticoduodenectomy (Whipple procedure); 2 patients required hepatic resection; and 1 patient had an orthotopic liver transplant. These 23 patients represent 30% of all patients evaluated in this study. Data on the histological margin status were available for 19 (83%) of these 23 patients. Fifteen patients (79%) underwent complete tumor resections with negative histological margins, whereas in 4 patients, there was microscopic residual disease. Interestingly, no statistically significant difference was found in the survival curves of these 2 groups (Figure 1). In 2 cases, a hepatic resection was necessary to ensure negative margins, and 1 patient with concomitant biliary cirrhosis underwent hepatic transplantation.

Perioperative morbidity occurred in 10 patients (18%). Of note, 14% (3 patients) in group 1 developed cholangitis, biliary obstruction, and intractable ascites, respectively, while hospitalized. The 30-day operative mortality was 6%, with 4 of 5 deaths occurring in patients undergoing noncurative procedures (Table 3). Overall median survival time and 5-year survival rate were 11 months and 23%, respectively (Figure 2). Group 1 patients had a median survival of 4 months, with 0% 5-year survivors. Patients in group 2 had a median survival of 8 months, and 10% survived 5 years. Patients in group 3, had a median survival of 72 months and a 5-year survival of 55%. Two patients died of recurrent disease after 5 years at 72 months and 78 months, respectively. Fourteen patients (22%) remain alive with a mean follow-up of 48 months.

Type of resection was the only independent variable found to demonstrate a significant effect on survival (Figure 3). Patient age, sex, tumor location, presence of jaundice, weight loss, abdominal pain, pruritus,
cholangitis, and admission of total bilirubin or alkaline phosphatase had no statistically significant impact on median or 5-year survival (Table 4).

Adenocarcinoma of the extrahepatic bile ducts, or cholangiocarcinoma, is a rare tumor. In autopsy studies, the incidence ranges between 0.01% and 0.5%.21-23 It is estimated that 6900 new cases of cancer of the extrahepatic bile ducts and gallbladder will be diagnosed in the United States in 2000.1 Although the exact cause remains unknown, several factors have been associated with the development of this malignant neoplasm: ulcerative colitis or primary sclerosing cholangitis, choledochal cysts, hepatolithiasis, parasitic infection, and chemical carcinogens.2 Because of its rarity, indolent growth pattern, lo-
cal invasiveness, and close proximity to vital structures challenging surgical resection, definitive guidelines regarding optimal surgical treatment and cure rates have been difficult to establish. There are quite disparate opinions in the literature regarding the resectability and curability of these tumors. However, recently there seems to be increasing support for an aggressive surgical approach to the treatment of cholangiocarcinoma.

The current study was conducted to examine the prognostic factors and outcomes in the treatment of cholangiocarcinoma at our institution. In the patient population evaluated, the clinical presentation and the pathologic features of these tumors were similar to those of previous reports. The distribution of tumor locations is also similar to those reported in several recent series. Although tumors located in the lower third enjoyed longer median survival and 5-year survival, this did not reach statistical significance. The literature is divided regarding the importance of tumor location as a prognostic variable. Several investigators have reported that tumors located in the lower third of the biliary tree have a more favorable prognosis, while others have found no differences in survival. This finding, however, may be attributable to the increased ability to remove all macroscopic disease with a pancreaticoduodenectomy compared with tumors found more distally.

Jaundice was the most common indicator, followed by weight loss and abdominal pain. The presence, absence, or degree to which these signs and symptoms were present demonstrated no significant impact on prognosis. This finding is similar to that of other large series on resections for cholangiocarcinoma, which found that
only those variables that correlate to the inability to remove all macroscopic disease (ie, residual tumor or positive lymph nodes) adversely affected survival.30,31 In fact, the only variable that affected survival in the current study was the ability to completely remove all macroscopic tumor at celiotomy. This finding corresponds with and corroborates several recent studies that have shown complete resection to prolong survival.24-26,32

The observation that margin status did not significantly impact survival can likely be explained by the small numbers of patients involved and the indolent growth pattern of these tumors.33 Pichlmayr et al32 in a large series from Germany also found that incomplete resection imparted a survival advantage, albeit less than a complete resection, and could lead to survival times greater than 5 years. This study, however, was able to accumulate 249 patients through a nationwide referral pattern. In the current series, only 4 patients who underwent a potentially curative resection had microscopically positive margins, and although survival was not found to be statistically different, all of these patients eventually succumbed to their disease. We would therefore agree with other authors that an aggressive policy of resection whenever possible in the treatment of these tumors is warranted, and that a complete resection is the best chance for cure and should be the goal of resectional therapy.25

In most of our patients, this was possible without the use of hepatic resection or transplantation; however, we have begun to more liberally use these procedures to assure negative histologic margins in those patients considered suitable candidates.

This aggressive approach is also warranted on the grounds that in the event that a complete resection cannot be performed, removal of all macroscopic disease alone imparts a significant survival advantage and would seem to be the best form of palliation. This study revealed a large survival advantage for patients undergoing a potentially curative tumor resection and a statistically significant survival advantage in patients with macroscopic disease left in situ or bypassed compared with nonoperative therapies. A review of the literature evaluating surgical vs non-surgical palliation does not reveal a consistent survival advantage for one form of palliation over another.34-39

Table 5 lists a survey of the published series since 1980 demonstrating rates of tumor resection and patient mortality and survival.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Resection Rate, %</th>
<th>Curative Resection Rate, %</th>
<th>Surgical Mortality, %</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tompkins et al</td>
<td>1981</td>
<td>47</td>
<td>47</td>
<td>...</td>
<td>23</td>
<td>Median, 11 mo</td>
</tr>
<tr>
<td>Tsuzuki et al</td>
<td>1983</td>
<td>31</td>
<td>52</td>
<td>...</td>
<td>0</td>
<td>2-year, 50%</td>
</tr>
<tr>
<td>Alexander et al</td>
<td>1984</td>
<td>109</td>
<td>26</td>
<td>92.3</td>
<td>38.5</td>
<td>Mean, 12.2 mo</td>
</tr>
<tr>
<td>Mizumoto et al</td>
<td>1986</td>
<td>26</td>
<td>43</td>
<td>30</td>
<td>17.9</td>
<td>Mean, 11.8 mo</td>
</tr>
<tr>
<td>Lai et al</td>
<td>1987</td>
<td>52</td>
<td>31</td>
<td>52</td>
<td>4</td>
<td>Median, 28 mo</td>
</tr>
<tr>
<td>Pison and Rossi</td>
<td>1988</td>
<td>156</td>
<td>16</td>
<td>52</td>
<td>0</td>
<td>4% (all patients)</td>
</tr>
<tr>
<td>Tsuzuki et al</td>
<td>1989</td>
<td>50</td>
<td>31</td>
<td>...</td>
<td>14</td>
<td>&lt;18%</td>
</tr>
<tr>
<td>Ouchi et al</td>
<td>1989</td>
<td>52</td>
<td>27</td>
<td>...</td>
<td>0</td>
<td>Median, 38 mo</td>
</tr>
<tr>
<td>Tompkins et al</td>
<td>1990</td>
<td>107</td>
<td>30</td>
<td>...</td>
<td>16</td>
<td>...</td>
</tr>
<tr>
<td>Nimura et al</td>
<td>1990</td>
<td>66</td>
<td>83.3</td>
<td>69.7</td>
<td>6.4</td>
<td>5-year, 40.5%</td>
</tr>
<tr>
<td>Boerma</td>
<td>1990</td>
<td>581</td>
<td>131</td>
<td>20.6</td>
<td>7.4</td>
<td>Median, 25 mo</td>
</tr>
<tr>
<td>Hadjis et al</td>
<td>1991</td>
<td>307</td>
<td>32</td>
<td>...</td>
<td>15.5</td>
<td>Median, 16-24 mo</td>
</tr>
<tr>
<td>Reding et al</td>
<td>1992</td>
<td>122</td>
<td>19</td>
<td>...</td>
<td>0</td>
<td>3-year, 50% (R0)</td>
</tr>
<tr>
<td>Childs and Hart</td>
<td>1993</td>
<td>31</td>
<td>55</td>
<td>...</td>
<td>6</td>
<td>Median, 13 mo</td>
</tr>
<tr>
<td>Nagorney et al</td>
<td>1993</td>
<td>171</td>
<td>60</td>
<td>72</td>
<td>4.3</td>
<td>Mean, 32 mo</td>
</tr>
<tr>
<td>Bar et al</td>
<td>1993</td>
<td>57</td>
<td>96.5</td>
<td>50.9</td>
<td>1.9</td>
<td>5-year, 23.2%</td>
</tr>
<tr>
<td>Tashiro et al</td>
<td>1993</td>
<td>46</td>
<td>73.9</td>
<td>73.5</td>
<td>2.9</td>
<td>5-year, 24.4%</td>
</tr>
<tr>
<td>Koyama et al</td>
<td>1993</td>
<td>20</td>
<td>...</td>
<td>25</td>
<td>...</td>
<td>Longest, 5, 6 mo</td>
</tr>
<tr>
<td>Schreinholzer et al</td>
<td>1994</td>
<td>129</td>
<td>32</td>
<td>53</td>
<td>9</td>
<td>Median, 16 mo</td>
</tr>
<tr>
<td>Myburgh</td>
<td>1995</td>
<td>31</td>
<td>85</td>
<td>79</td>
<td>9.3</td>
<td>Median, 23.2 mo</td>
</tr>
<tr>
<td>Washburn et al</td>
<td>1996</td>
<td>339</td>
<td>45</td>
<td>76</td>
<td>9.9</td>
<td>Median, 25 mo</td>
</tr>
<tr>
<td>Klopman et al</td>
<td>1996</td>
<td>249</td>
<td>60</td>
<td>10.5-12.7</td>
<td>Median, 15.5-19.9 mo</td>
<td></td>
</tr>
<tr>
<td>Chung et al</td>
<td>1998</td>
<td>40</td>
<td>60</td>
<td>23</td>
<td>...</td>
<td>5-year, 0%-28%</td>
</tr>
<tr>
<td>Burke et al</td>
<td>1998</td>
<td>90</td>
<td>77</td>
<td>43</td>
<td>7</td>
<td>Median, 40 mo</td>
</tr>
<tr>
<td>Launois et al</td>
<td>1999</td>
<td>94</td>
<td>...</td>
<td>43</td>
<td>12.5</td>
<td>5-year, 27.3%</td>
</tr>
<tr>
<td>Current study</td>
<td>2000</td>
<td>77</td>
<td>71</td>
<td>42</td>
<td>6</td>
<td>Median, 72 mo</td>
</tr>
</tbody>
</table>

* Ellipses indicate data not available.
ologic margins. If this is not possible, complete resection of all macroscopic disease seems to improve survival and provide optimal palliation of jaundice and its sequelae. Even patients in whom residual tumor must be left behind or on whom a surgical bypass must be performed experience a statistically significant increase in survival over nonoperative therapies. This surgical approach can be conducted with low perioperative morbidity rates and mortalities.

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Reprints: Seymour I. Schwartz, MD, FACS, Department of Surgery, School of Medicine and Dentistry, University of Rochester, 601 Elmwood Ave, Rochester, NY 14642.

REFERENCES