Clinical Behavior and Prognostic Factors of Periampullary Adenocarcinoma

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Objective
The authors evaluated the outcome and potential prognostic factors of 60 patients with surgically resected periampullary tumors.

Summary Background Data
Periampullary carcinomas exhibit different clinical behaviors according to their site of origin. There are no prognostic factors for deciding the type of surgery to be used or for choosing patients with tumors that have a poor prognosis for adjuvant treatment.

Methods
A retrospective review was performed of 15 clinical and pathologic variables encountered among 60 patients with periampullary tumors. Tumors were divided into four groups according to their site of origin. Kaplan–Meier survival curves of the four groups were plotted and differences were evaluated with the log-rank test. Cox’s proportional hazards model was used to test for separate and combined independent predictors of disease-free survival.

Results
Twenty-nine ampullary carcinomas, 20 ductal pancreatic carcinomas, 7 distal common bile duct carcinomas, and 4 carcinomas of the periampullary duodenum were found. Five-year disease-free survival was 43%, 0%, 0%, and 75%, respectively. According to the Cox analysis, absence of neural invasion and use of adjuvant chemotherapy were significant factors for longer survival of patients with ampullary tumors. Lymphatic invasion was related to a shorter survival in patients with pancreatic carcinoma.

Conclusions
Five-year disease-free survival of patients with periampullary tumors is related to tumor type. Prognosis was better for ampullary tumors if neural invasion was absent and if adjuvant chemotherapy was used. Lymphatic invasion was associated with a shorter recurrence-free survival among patients with pancreatic carcinoma.
Periampullary adenocarcinoma may arise from the mucosa of the ampulla of Vater, the pancreatic duct, the distal common bile duct, or the duodenum. Carcinomas originating from each of these sites exhibit different clinical behaviors.1,4

Despite radical surgical resection, the prognosis for most patients with periampullary carcinomas, particularly pancreatic ductal adenocarcinoma, is frustrating,5,6 however, a few long-term survivors have been identified. As with most malignant diseases, it is important to identify those patients who might survive for only a few months after pancreatectomy versus those for whom surgical resection would lead to long-term survival or cure.

If reliable prognostic factors can be identified before surgery, then the choice of surgery—pancreatectomy or a palliative procedure—would be made easier, and such identification and may even be valuable in choosing patients with tumors with poor prognostic factors for adjuvant treatment.

Our aim in the current study was to explore differences in the clinical evolution of pancreatic and periampullary carcinomas and to evaluate potential prognostic factors.

METHODS

Of 417 patients with pancreatic and periampullary carcinoma who underwent surgery for palliation or resection at the Instituto Nacional de la Nutrición between 1960 and 1991, 60 patients were selected for analysis. This group represents all survivors of a potentially curative procedure (pancreatoduodenectomy or total pancreatectomy) during the study period.

A retrospective review of clinical histories and pathologic specimens of these patients was performed, and 15 different variables were analyzed. Resected specimens were re-examined by one of us (L.Q.) and tumors were divided into four groups according to the site of origin.

Thirty-six formalin-fixed, paraffin-embedded archival samples were available for nuclear DNA content analysis through use of flow cytometric studies.7,8 DNA histogram patterns were analyzed without knowledge of the clinical course of the disease.

Kaplan–Meier survival curves of the four groups were plotted,9 and the log-rank test10 was used to detect differences among survival curves. Cox's proportional hazards model was used to test for separate and combined independent predictors of disease-free survival.11

RESULTS

Twenty-nine ampullary carcinomas, 20 ductal pancreatic carcinomas, 7 distal common bile duct carcinomas, and 4 carcinomas of the periampullary duodenum were found. Whipple's procedure was performed in the vast majority of cases. Only four patients, three with pancreatic and one with ampullary carcinoma, underwent total pancreatectomy. Most tumors were well or moderately differentiated among the four groups. General characteristics of the four groups are shown in Table 1. Tumor invasion to adjacent organs and microscopic invasion to blood vessels, lymphatic vessels, and nerves is discussed in Table 2.

Negative margins were obtained in 97%, 90%, 100%, and 100% of cases, respectively, for ampullary, pancreatic, biliary, and duodenal tumors. In three cases, pancreatic transection was the site of positive margins, namely, two pancreatic tumors and one 8-cm ampullary tumor with extensive pancreatic invasion.

Adjuvant chemotherapy involving predominantly 5-fluorouracil, mitomycin, and doxorubicin was administered to 45% of patients with ampullary tumors, 5% of patients with pancreatic tumors, and 29% of patients with common bile duct tumors. The combination of 5-fluorouracil as a radiosensitizer and 40 Gy of radiotherapy was administered to 3% of ampullary tumors and 37% of pancreatic tumors.

In the group of patients with ampullary carcinoma, eight tumors were diploid and nine tetraploid, whereas most pancreatic tumors were diploid. The comparative ploidy distribution is shown in Figure 1.

Median survival for patients with pancreatic, ampullary, and bile duct carcinoma was 18, 9, and 24 months, respectively. As for duodenal carcinoma, The last follow-up of patients with duodenal carcinoma was at 360 months, at which time a 75% survival rate was determined. Survival of patients according to type of carci-

<table>
<thead>
<tr>
<th>Table 1. GENERAL CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampulla (n = 29)</td>
</tr>
<tr>
<td>Mean age ± SD (years)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
</tr>
<tr>
<td>Size (cm)</td>
</tr>
<tr>
<td>Node metastases (%)</td>
</tr>
<tr>
<td>Local invasion (%)</td>
</tr>
<tr>
<td>Histologic differentiation (%)</td>
</tr>
<tr>
<td>Good</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Poor</td>
</tr>
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A tumor is summarized in Figure 2. Differences among 5-year survival rates were marginally significant according to the log-rank test (p = 0.05).

Because only a small number of patients had tumors of the distal common bile duct and duodenum, only the group of patients with pancreatic and ampullary carcinomas were considered for the risk-factor analysis. The separate associations between several clinical, surgical, and pathologic characteristics with the time to recurrence of patients with pancreatic and ampullary tumors is presented in Table 3.

In the group of patients with pancreatic carcinoma, disease-free survival was related to lymph node metastases, which were observed in 10 of the 20 patients. A statistically significantly improved survival rate was observed in patients with negative lymph nodes compared with patients with positive lymph nodes (Fig. 3).

In the group of patients with ampullary carcinoma, shorter survival was significantly associated with neural invasion and use of adjuvant chemotherapy. Figure 4 shows survival curves for the groups of patients in whom none, one, or both of these factors were present. Differences among these curves reached statistical significance (p = 0.007).

**DISCUSSION**

**Pancreatic Ductal Adenocarcinoma**

Prognosis of patients with ductal adenocarcinoma of the pancreas is generally poor. Worldwide, the resectabil-

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**Figure 1.** Distribution of nuclear DNA ploidy patterns according to tumor location.

**Figure 2.** Kaplan-Meier disease-free survival curves of resected periampullary cancer plotted by tumor location.

**Table 2.** TUMOR INVASION

<table>
<thead>
<tr>
<th>Location</th>
<th>Ampulla (n = 29)</th>
<th>Pancreas (n = 20)</th>
<th>Bile Duct (n = 7)</th>
<th>Duodenum (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood vessels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nerves</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphatic vessels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* n = 25.
† n = 19.

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**Table 3.** UNIVARIATE COX REGRESSION ANALYSIS OF POTENTIAL PREDICTORS OF DISEASE-FREE SURVIVAL IN PANCREATIC AND AMPULLARY CARCINOMA

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hazard Ratio Pancreas</th>
<th>p</th>
<th>Hazard Ratio Ampulla</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>3.60</td>
<td>0.1</td>
<td>0.56</td>
<td>0.3</td>
</tr>
<tr>
<td>Age</td>
<td>1.02</td>
<td>0.6</td>
<td>1.00</td>
<td>1.0</td>
</tr>
<tr>
<td>Tumor size</td>
<td>1.00</td>
<td>1.0</td>
<td>1.21</td>
<td>0.2</td>
</tr>
<tr>
<td>Lymph node metastases</td>
<td>8.19</td>
<td>0.06</td>
<td>1.28</td>
<td>0.6</td>
</tr>
<tr>
<td>Local invasion</td>
<td>3.78 x 10^5</td>
<td>1.0</td>
<td>1.04</td>
<td>1.0</td>
</tr>
<tr>
<td>Complete resection</td>
<td>0.55</td>
<td>0.5</td>
<td>0.11</td>
<td>0.01*</td>
</tr>
<tr>
<td>Pathologic differentiation</td>
<td>1.25</td>
<td>0.6</td>
<td>1.52</td>
<td>0.3</td>
</tr>
<tr>
<td>Microscopic invasion to</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nerves</td>
<td>0.36</td>
<td>0.4</td>
<td>3.14</td>
<td>0.04</td>
</tr>
<tr>
<td>Blood vessels</td>
<td>1.77</td>
<td>0.5</td>
<td>3.09</td>
<td>0.2</td>
</tr>
<tr>
<td>Lymphatic vessels</td>
<td>0.24</td>
<td>0.2</td>
<td>1.82</td>
<td>0.3</td>
</tr>
<tr>
<td>Signet ring cells</td>
<td>1.66 x 10^-16</td>
<td>1.0</td>
<td>0.73</td>
<td>0.8</td>
</tr>
<tr>
<td>Epidermoid differentiation</td>
<td>5.58 x 10^-16</td>
<td>1.0</td>
<td>6.15</td>
<td>0.1</td>
</tr>
<tr>
<td>Ploidy</td>
<td>4.32 x 10^-15</td>
<td>1.0</td>
<td>2.21</td>
<td>0.3</td>
</tr>
<tr>
<td>% of phase “S” cells</td>
<td>1.22</td>
<td>0.1</td>
<td>1.01</td>
<td>0.8</td>
</tr>
<tr>
<td>Adjuvant radiotherapy</td>
<td>1.55</td>
<td>0.5</td>
<td>1.07</td>
<td>1.0</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>0.84</td>
<td>0.8</td>
<td>0.32</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* Difference determined by one patient.
ity rate for ductal adenocarcinoma of the pancreas ranges between 5% and 15%, morbidity and mortality rates are relatively high, and the 5-year survival rate is 4% to 7%.12 During the 1960s and 1970s, the hospital mortality rate associated with pancreaticoduodenectomy was approximately 25%.13 This rate changed dramatically during the 1980s, and many centers now report hospital mortality rates of less than 5%.14,15 However, despite improvements in surgical morbidity and mortality rates, even when the tumor can be resected and there is no evidence of regional or distant metastases, only a few patients survive 3 years or more after resection.5,6

Several researchers have sought to identify the determinants of long-term survival among patients with resectable adenocarcinoma of the pancreas. Factors associated with poor survival after resection have included perioperative blood transfusions, lymph node metastases, aneuploid DNA content, and increased tumor size.16–18

Geer and Brennan, using both multivariate and univariate analysis in a study of 146 patients whose condition was cured by resection, found that tumors with poor histologic differentiation, tumors larger than 2.5 cm, and lymph node involvement were predictors of significantly worse survival.19

In contrast, in 1986 authors from the Mayo Clinic (Rochester, Minnesota) published a retrospective study of 79 patients with ductal adenocarcinoma of the pancreas and analyzed 33 clinical and 38 pathologic variables.20 In this study, certain histopathologic characteristics, such as Broder’s grades 3 and 4 in the primary tumor, a round-cell infiltrate at the tumor margin, and epithelial atypia in the uninvolved pancreatic duct, were significantly associated with a poor prognosis. We believe these variables to be relatively unimportant because they are unidentifiable before surgery.

Years later, other investigators from the Mayo Clinic studied the relationship between DNA ploidy patterns and survival.21 They found no difference in the DNA content analysis of patients with pancreatic ductal adenocarcinoma when comparing long-term and short-term survival after resection.

In the current study, using both separate and combined analysis, we found lymph node invasion to be the only independent factor for prognosis. This observation is in accordance with the results found by Geer and Brennan in their study at Memorial Sloan-Kettering Cancer Center (New York, New York).19

**Ampullary Carcinoma**

Carcinoma of the ampulla of Vater represents 4% to 10% of patients with peripancreatic carcinoma and 0.2% of patients with malignant tumors of the gastrointestinal tract found at autopsy.22 The ampullary carcinoma tumor accounts for 10.2% to 36% of all surgically operable pancreaticoduodenal tumors.

The clinical course of patients with ampullary carcinoma has been recognized to be more favorable than that of patients with carcinoma of the pancreas. Researchers from the Johns Hopkins Hospital (Baltimore) reported a 36% 5-year survival rate for 19 patients with ampullary carcinoma who had undergone pancreaticoduodenectomy, whereas for 50 patients with pancreatic carcinoma who had undergone a similar procedure, the 5-year survival rate was 18%.23

Survival has generally been considered to be related to tumor size, degree of local invasiveness of the primary tumor, presence of lymph node metastases, perineural invasion, and degree of cellular differentiation.24 Matory et al. conducted a study involving 69 patients with ampullary carcinoma at the Memorial Sloan-Kettering Cancer Center and evaluated several factors for their influence on survival: tumor extension, lymph node me-
tastases, margins, size, and resectability. Of these, resectability was found to be the only influencing factor. The median survival time for patients who underwent resection (51 months) was more than twice that of patients who did not undergo resection (8 months).

Recently, investigators at the Massachusetts General Hospital (Boston) conducted a study of 41 patients with ampullary carcinoma. Twelve patients with well- or moderately differentiated tumors limited to the ampulla or duodenum and with uninvolved lymph nodes and resection margins had 5-year local control and survival rates of 100% and 80%, respectively. In contrast, 17 patients with poorly differentiated tumors that had invaded the pancreas and with involved lymph nodes or positive resection margins had local control and survival rates of 50% and 38%, respectively. For 12 patients within this "high-risk" group (i.e., the group of 17 patients with poorly differentiated tumors) who also received postoperative radiation therapy after pancreatectomy, better local control usually resulted (83%), although survival did not improve.

To minimize the development of local recurrence, physicians have used adjuvant therapy for patients with ampullary carcinoma. Barton and Copeland reported their experience at the University of Texas M.D. Anderson Center (Houston) regarding 56 patients with carcinoma of the ampulla of Vater. Twenty-two of these patients initially underwent biliary tract decompression, and 44 underwent pancreaticoduodenectomy. Seventeen patients received postoperative chemotherapy, in which 5-fluorouracil was the most common agent used in combination with doxorubicin, carmustine, vincristine, methyl-lomustine, or mitomycin. Sixteen patients (94%) had previously undergone a pancreaticoduodenectomy. Although no analysis was presented, the authors stated that "no combination of drugs appeared to prolong life when used in either the adjuvant or therapeutic setting." In contrast, Yeung and colleagues found no residual tumor in specimens of pancreaticoduodenectomy performed for four patients with duodenal/ampullary carcinomas who had received neoadjuvant chemoradiation therapy.

Our study showed better prognosis of ampullary carcinomas compared with pancreatic tumors and suggests that certain variables, such as the presence of neural invasion and the use of chemotherapy, influence prognosis. We agree that adjuvant and neoadjuvant therapies should be tested in controlled studies for this particular type of tumors.

Lower-Third Biliary Carcinoma

The location of the lesion appears to be the most important prognostic factor. Lesions in the lower third of the biliary tract are the most resectable and are therefore associated with better results. The 5-year survival rate of patients in a study conducted by Tompkins et al. at the University of California at Los Angeles was 28%. Recently, a study of distal-third biliary tumors at the Lahey Clinic (Boston, MA) resulted in 100% resectability. The median survival time was 16 months, and the 5-year survival rate was 20%.

In a recent study from Japan, the researchers analyzed the influence of various clinicopathologic factors on survival for 70 patients who underwent resection for bile duct carcinoma Japan. A univariate analysis revealed 10 factors associated with a significant outcome. However, when the interactive effects of these factors were considered, a multivariate analysis using Cox's stepwise proportional hazards model was performed and revealed pancreatic invasion and perineural invasion to be the most significant prognostic factors.

Tompkins et al. found several factors to be responsible for a favorable outcome in their patients with bile duct carcinoma, but pancreatic and perineural invasion were not among these factors.

Duodenal Carcinoma

Primary duodenal carcinoma accounts for 0.3% of all gastrointestinal malignancies. It is found in only 0.035% of autopsies. Its rarity has made the understanding of the biology of this tumor difficult. The 10-year survival rate of 20 patients treated at Kansas Medical Center (Kansas City, KS) between 1975 and 1990 was 67%.

Because we included only seven lower-third biliary tumors and four duodenal tumors in our series, we were unable to investigate potential prognostic factors in these two groups.

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References


