Pancreaticoduodenectomy Is Curative in the Majority of Patients With Node-Negative Ampullary Cancer

Kimberly M. Brown, MD; Andrew J. Tompkins; Sherri Yong, MD; Gerard V. Aranha, MD, FRCSC; Margo Shoup, MD

Hypothesis: Survival following resection for ampullary carcinoma may be influenced by 1 or more clinical or pathologic variables.

Design: Retrospective medical records review.

Setting: Academic tertiary care center.

Patients: From July 1, 1991, through April 30, 2004, 72 patients (31 males and 41 females) were treated for ampullary carcinoma at Loyola University Medical Center, Maywood, Ill. Of these, 51 patients who underwent potentially curative pancreaticoduodenectomy were studied.

Interventions: Whipple procedure for attempted cure in 51 patients with ampullary adenocarcinoma.

Main Outcome Measures: The effects of clinical and pathologic factors on disease-specific survival were analyzed using log-rank and a multivariate Cox proportional hazards model.

Results: The median age of the 51 patients (25 males and 26 females) was 69 years (age range, 38-90 years). Median operative time was 6 hours (range, 4-12 hours), and median estimated blood loss was 800 mL (range, 350-7500 mL). Thirty-day mortality was 2% (1 of 51 patients). Twenty-seven had node-negative disease, 34 cases were T1/T2, and 23 were well differentiated. Median follow-up for patients still alive was 42 months (range, 2-147 months); overall 5-year disease-specific survival was 58%. Five-year survival was 78% (21/27) in node-negative patients, 73% (25/34) for T1/T2 patients, and 76% (17/23) for well-differentiated tumors compared with 25% for node-positive, 8% for T3/T4, and 36% for poorly or moderately differentiated tumors (P<.01). On multivariate analysis, only node-negative disease maintained significance (hazard ratio, 5.2; 95% confidence interval, 1.2-21.9). In all groups, there were no deaths due to disease after 3 years of survival was reached.

Conclusion: Pancreaticoduodenectomy is curative in 80% of patients with node-negative ampullary carcinomas. Once 3-year survival is reached, long-term survival can be expected.

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erative time was 6 hours (range, 4-12 hours). Median receiving a biliary stent during this procedure.

Retrograde cholangiopancreatography as part of their pre-
treatment. Thirty-nine patients (76%) underwent endoscopic
abdominal pain in 14 (27%), and weight loss in 12 (23%).

The symptoms of these 51 patients were jaundice in 41 (80%),
abdominal pain in 14 (27%), and weight loss in 12 (23%).

The median age at diagnosis was 69 years (age range, 38-90 years). The most common presenting symptoms of these 51 patients were jaundice in 41 (80%), abdominal pain in 14 (27%), and weight loss in 12 (23%). Seven patients (14%) were asymptomatic at presentation. Thirty-nine patients (76%) underwent endoscopic retrograde cholangiopancreatography as part of their preoperative workup, with 30 (77%) of these patients receiving a biliary stent during this procedure.

All patients underwent a standard PD. The median operative time was 6 hours (range, 4-12 hours). Median estimated blood loss was 800 mL (range, 350-7500 mL). A median of 0 U of packed red blood cells were transfused (range, 0-7 U).

Thirty-day mortality was 2% (1 of 51 patients). This patient had been discharged home but returned with massive upper gastrointestinal tract bleeding. The patient ultimately went into multiorgan system failure and was allowed to die. Overall morbidity was 47% (24 of 51 patients). Fifteen patients (29%) developed a pancreatic fistula, 5 (9.6%) had wound infections, 4 (7.8%) had intra-abdominal abscesses, 3 (6%) had delayed gastric emptying, and 2 (4%) developed pneumonia. There were 5 patients (10%) with more than 1 complication. Median length of stay was 10 days (range, 6-39 days).

Pathology data are summarized in Table 2. Median tumor size was 2.1 cm (range, 0.6-5.2 cm). Thirty-four patients (67%) had Tis or T1 tumors, while 17 patients (33%) had T3 or T4 tumors. There were no gross or microscopic positive margins. Twenty-three patients (45%) had well-differentiated tumors, and 23 patients (45%) had moderately or poorly differentiated histology. Twenty-four patients (47%) had tumor metastasis to 1 or more lymph nodes. The median number of positive lymph nodes was 2 (range, 1-11). A median of 15 nodes per patient were examined, with a range of 4 to 35 nodes.

Estimated disease-specific 5-year survival for the cohort was 58%. For patients alive at the time of study, median follow-up was 42 months (range, 2-147 months). Factors found to significantly influence survival on univariate analysis were lymph node metastasis, tumor stage, and well-differentiated histology (Table 3). Median survival for patients with positive lymph nodes was 20 months. Median survival for patients with T3 or T4 tumors was 18 months. For patients with moderately or poorly differentiated tumors, median survival was 32.4 months. The median survivals for patients with negative lymph nodes, T1/T2 tumors, and well-differentiated histology have not yet been reached.

Multivariate analysis demonstrated that only lymph node metastasis maintained a significant association with survival. Seventy-eight percent of patients with negative lymph nodes remained alive at 5 years while only 25% of patients with positive lymph nodes survived (P = .02) (Figure). Of those patients with positive lymph nodes, there was no correlation between the number of positive lymph nodes and survival. No patient died in either group more than 3 years after resection.

### Table 1. Demographic and Perioperative Data*

<table>
<thead>
<tr>
<th>Age, y</th>
<th>69 (38-90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative time, h</td>
<td>6 (4-12)</td>
</tr>
<tr>
<td>Estimated blood loss, mL</td>
<td>800 (350-7500)</td>
</tr>
<tr>
<td>PRBCs transfused, U</td>
<td>0 (0-7)</td>
</tr>
<tr>
<td>Length of stay, d</td>
<td>10 (6-39)</td>
</tr>
<tr>
<td>30-d mortality†</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Overall morbidity†</td>
<td>24 (47)</td>
</tr>
<tr>
<td>Pancreatic fistula†</td>
<td>15 (29)</td>
</tr>
<tr>
<td>Wound infection†</td>
<td>5 (9.6)</td>
</tr>
<tr>
<td>Intra-abdominal abscess†</td>
<td>4 (7.8)</td>
</tr>
<tr>
<td>Delayed gastric emptying†</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Pneumonia†</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

*All data are reported as median (range) unless otherwise indicated.

†Data are given as the number (percentage) of 51 patients.

### Table 2. Pathologic Characteristics of 44 Resected Specimens*

<table>
<thead>
<tr>
<th>Size, median (range), cm</th>
<th>2.1 (0.6-5.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis/T1</td>
<td>10 (20)</td>
</tr>
<tr>
<td>T2</td>
<td>24 (47)</td>
</tr>
<tr>
<td>T3</td>
<td>11 (22)</td>
</tr>
<tr>
<td>T4</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Lymph node metastases</td>
<td>24 (47)</td>
</tr>
<tr>
<td>No. of positive nodes, median (range)</td>
<td>2 (1-11)</td>
</tr>
</tbody>
</table>

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**METHODS**

Following approval by the Loyola University institutional review board, Maywood, Ill, pathology records and cancer registry data were searched for patients treated for AC from July 1, 1991, through April 30, 2004. Hospital medical records were reviewed to collect demographic and perioperative data. Follow-up and survival were determined by searching cancer registry records, outpatients' medical records, and the Social Security death index searchable database (available at: http://ssdi.genealogy.rootsweb.com). All pathologic specimens were reviewed by a single pathologist (S.Y.) who was blinded to the clinical and survival data, and a diagnosis of AC was confirmed.

Statistical analyses were calculated using SPSS for Windows, version 10.0 (SPSS Inc, Chicago, Ill). The association of categorical variables and survival was assessed using the Kaplan-Meier method, and the significance was tested using the log-rank test. For those factors found to be significant in univariate analyses, a multivariate analysis using a Cox proportional hazards regression model was used to determine significant influence on survival. Statistical significance was determined for P < .05.

**RESULTS**

During the study period, 72 patients (31 males and 41 females) were treated for AC at our institution. Of these patients, 11 underwent noncurative procedures. Five patients did not have AC on a second review of pathology slides, and 5 were lost to follow-up or had incomplete records. A total of 51 patients (25 males and 26 females) who underwent PD were included in the current study.

Demographic and perioperative data are summarized in Table 1. The median age at diagnosis was 69 years (age range, 38-90 years). The most common presenting symptoms of these 51 patients were jaundice in 41 (80%), abdominal pain in 14 (27%), and weight loss in 12 (23%). Seven patients (14%) were asymptomatic at presentation. Thirty-nine patients (76%) underwent endoscopic retrograde cholangiopancreatography as part of their preoperative workup, with 30 (77%) of these patients receiving a biliary stent during this procedure.

All patients underwent a standard PD. The median operative time was 6 hours (range, 4-12 hours). Median estimated blood loss was 800 mL (range, 350-7500 mL). A median of 0 U of packed red blood cells were transfused (range, 0-7 U).

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Pathology data are summarized in Table 2. Median tumor size was 2.1 cm (range, 0.6-5.2 cm). Thirty-four patients (67%) had Tis or T1 tumors, while 17 patients (33%) had T3 or T4 tumors. There were no gross or microscopic positive margins. Twenty-three patients (45%) had well-differentiated tumors, and 23 patients (45%) had moderately or poorly differentiated histology. Twenty-four patients (47%) had tumor metastasis to 1 or more lymph nodes. The median number of positive lymph nodes was 2 (range, 1-11). A median of 15 nodes per patient were examined, with a range of 4 to 35 nodes.

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Multivariate analysis demonstrated that only lymph node metastasis maintained a significant association with survival. Seventy-eight percent of patients with negative lymph nodes remained alive at 5 years while only 25% of patients with positive lymph nodes survived (P = .02) (Figure). Of those patients with positive lymph nodes, there was no correlation between the number of positive lymph nodes and survival. No patient died in either group more than 3 years after resection.
Ampullary carcinoma remains an uncommon periampullary tumor with a more favorable prognosis than other tumors arising in this region. The improved prognosis relative to pancreatic and biliary cancers is thought to result in part from a relatively higher rate of resectability. Of our original cohort, only 15% (11/72) were not candidates for curative resection, which is in agreement with most reported studies.2,6,18,19

Several authors have emphasized the importance of pathologic re-review of patients considered to have AC.2,20 Other periampullary tumors have different prognoses; therefore, confirmation of ampullary origin ensures optimal accuracy. Our study excluded 5 (7% of the original cohort) of 71 patients who did not have AC on pathology review, and 5 patients (7% of the original cohort) who were originally treated for AC but did not have pathology slides for review, complete perioperative data, or who were lost to follow-up.

Many predictive factors have been reported to influence survival in AC, including resection,21 lymph node metastases,22,23 margin status,6,24 tumor stage,18 tumor grade,20 lymphatic invasion,20 perineural invasion12 and blood transfusion.6 On our multivariate analysis, only lymph node metastases maintained status as an independent predictor of survival. This is in agreement with a large series from Memorial Sloan-Kettering, which demonstrated on multivariate analysis that resection, negative margins, and negative lymph nodes were significant independent positive prognostic factors.2 The number of involved lymph nodes has been shown to influence survival in tumors such as colorectal cancer.25 In our study of AC, there was no difference in survival based on the number of lymph nodes involved with metastatic disease. Others have shown a difference in outcome based on the number and location of positive lymph nodes in AC.17,22 Our study may be underpowered to detect these differences. Forty-seven percent of our patients had lymph node metastases, which compares with reported incidences of 30% to 50%.2,6,18,24 None of our patients who underwent resection had a positive margin, so this factor could not be analyzed.

Survival for patients with AC ranges from 23% to 59%, with a trend toward improved survival in recent studies.16,18,23,24 Many of the published series contain patients treated in the 1970s and earlier. Our study represents a series of patients treated since 1990, with an operative mortality of 2%, which is consistent with the current literature on PD.2,11,12 Our 5-year disease-specific survival of 58% is within the range of AC survivals reported in recent series.

When only node-negative patients are considered, PD is associated with a potential cure in 80% of the cases. In all of our patients, both with and without involved lymph nodes, there were no deaths from disease after 3 years. This correlates with recent data from Japan examining patterns of failure in AC, which noted a mean time to relapse of 13 months, with a range of 0.7 to 33 months.26 Benign lesions are reported to have longer intervals during which recurrences are identified, and local resections may have a longer time to recurrence.27 This information can be used to direct follow-up surveillance.

The use of ampulectomy for small tumors of the ampulla remains controversial. Some authors advocate this procedure for T1 lesions, with preoperative endoscopic biopsy, endoscopic ultrasound, and intraoperative frozen section as the procedures of choice to identify appropriate lesions.18,20 However, the reported sensitivity of preoperative
biopsy is only 42% to 76%. One of these groups also reported that endoscopic ultrasound correctly staged 9 of 12 lesions, and 3 of 3 adenocarcinomas.

Histologic evidence of invasion of the duodenal muscular propria has been shown to predict the presence of lymph node metastasis and could thus be used to make intraoperative decisions regarding the use of local excision vs PD. However, the status of the lymph nodes cannot be ascertained in a local excision, and the prognostic information regarding the presence of tumor in the lymph nodes would be lost. In addition, the potentially therapeutic value of removing involved lymph nodes makes complete resection the operation of choice for all patients who can otherwise tolerate the procedure. In our series, no patient with a T1 tumor had lymph node involvement; however, it is our policy to treat all resectable ACs with a PD for the reasons listed earlier.

CONCLUSIONS

Pancreaticoduodenectomy is curative in most patients with node-negative AC. This procedure may be associated with cure in 20% of patients with node-positive AC. Regardless, long-term survival can be expected once the 3-year mark has been reached. The addition of adjuvant therapy to node-positive patients should be evaluated in an attempt to improve survival in this group.

DISCUSSION

Michael Farnell, MD, Rochester, Minn: Dr Brown and her colleagues reviewed 51 patients undergoing potentially curative PD for AC. Clinopathologic factors were analyzed in both a univariate and multivariate methods to determine the effect of these variables on survival. They were careful to include only patients with AC as pathologic review was performed in all cases and if not of ampullary epithelial origin, they were excluded. The mortality was a commendable 2% and the morbidity of 48% is in keeping with contemporary reports for Whipple resection. Median follow-up for the patients still alive was 2.2 months and the overall 5-year actuarial survival was 58%. In the univariate analysis, node negativity, tumor size, and tumor differentiation correlated with survival while in the multivariate analysis only node negativity maintained significance. This is an important topic as AC is the second most common perianpillary tumor and the vast majority of patients are resectable at the time of operation. The authors point out, and the literature supports, that the survival following resection for AC is improving. In the article, the authors recommend PD for all patients with AC. While the authors found only one factor, that is, nodal status, to be significant in their multivariate model,
other series in the literature with a larger number of patients and longer median follow-up have variously reported that tumor size, differentiation, use of blood transfusion, perineural invasion, invasion into the pancreas, and adjuvant therapy all have prognostic implications with regard to survival.

I do have concerns regarding the main conclusion of the article. The authors state that there were no deaths in either node-negative or node-positive patients beyond 3 years and they equate 3-year survival with cure. They further imply that once the 3-year anniversary is reached, there are implications with regard to surveillance. Please note that there were only 44 patients in this study and the median follow-up for surviving patients was only 42 months.

Monson et al reported the Mayo experience with 104 patients undergoing radical resection for AC with a median follow-up of 7.4 years. (Cancer. November 1991;68:1863-1868). In that study, while most deaths occurred within the first 5 years following resection, 8 patients died of recurrent tumor more than 5 years postoperatively.

I have the following questions for the authors: (1) Five patients were excluded because on a second review they did not have AC. What criteria did your pathologist use to differentiate the epithelium of origin of the neoplasm; that is, bile duct, duodenum, pancreas, ampulla? (2) What about the 12 patients that were excluded because they were lost to follow-up? Did you search the social security death index database to see if any of these patients died greater than 3 years after operation? (3) You suggest that your data have implications with regard to follow-up surveillance. What is your surveillance program and how has it changed as a result of this investigation?

Dr Aranha: Your first question was regarding how we confirmed the presence of AC. We have a dedicated pathologist and the name was up on the slide, Sherry Young, who does all the pathology for us. She injects the pancreatic duct with blue dye and then dissect the pancreatic duct and its major branches. The cuts are made perpendicular to the duct starting at the ampulla and extending up the common duct and the pancreatic duct. In fact, she submits 30 sections per specimen. The specimens are first examined for carcinoma in situ and then for dysplasia and the mucosa in which these changes are noted are identified as the origin of the neoplastic process. If there is a question about the origin of the tumor, she uses keratin staining which is not 100% accurate, but if cytokeratins 7 and 20 are positive, then it is most likely that these are pancreatic in origin. So I believe a dedicated gastrointestinal pathologist is important.

You asked about the 12 patients that were lost to follow-up. No, we did not look at the death index on these patients. We felt that we needed to have all the data on these patients and going by the tumor registry data alone, we felt it was unfair to include these patients.

Finally, I think you also spoke about the possibility of patients failing beyond 5 years, and I think I agree with you on that. I think maybe we should change our statement in the article to say that if you live beyond 3 years, you are not going to get everlasting life. Maybe we should say that if a patient lives beyond 3 years, they have a good chance of living 5 years with further follow-up; it is possible we might have late failures.

And your last question was regarding follow-up. Dr Shoup, who is my partner now in the Section of Surgical Oncology, and I do not feel there is a standard follow-up for these patients around the country. We do have the patient get CT [computed tomography] scans yearly for the first 3 years, and if there is no evidence of recurrence, we will go to longer intervals. If you do a local resection for those who have Gardner syndrome or familial adenomatous polyposis, you have to add the upper gastrointestinal tract to your surveillance. Those patients, of course, are not part of this study.

Dr Aranha, MD: I think, and most others agree, that the high incidence of leak in AC is due to the texture of the gland. In a recent presentation to the Society of Surgery of the Alimentary Tract, the group from Johns Hopkins took patients with a soft pancreas used fibrin glue in half and no fibrin glue on the other around the pancreatic anastomosis. They found no difference in the leak rate in either group. The leak rate in that study was in the neighborhood of 40%. Our rate was 25%.

Your second question asked about how we manage leaks? We leave the pancreatic drain in and allow the patient to eat. If the volume of the drainage does not go up, they are allowed to go home with the drain and the drain is pulled when the leak dries up. But if the volume of the leak increases after they eat, then they are taken off food and given TPN [total parenteral nutrition]. Of course, patients who have full-blown peritonitis have to undergo surgical exploration. We have not had any of those.

You also asked about the type of pancreatic anastomosis. Because of a personal bias, I do a pancreaticogastrostomy. The other surgeons do a pancreaticojejunostomy. There was no difference in leakage rates in either group.

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Norman Estes, MD, Peoria, IL: Dr Aranha, it is a pleasure to again learn from your series in pancreatic diseases. Did you know when the operating surgeon thought they were dealing with pancreatic cancer, but later found out from the pathologist that the diagnosis was AC? This may have some importance in terms of how some people would treat pancreatic cancer if they are nihilistic when nodes are involved. I noticed that you had some surviving patients with extensive lymphatic spread. How would you treat a suspected pancreatic cancer that appears to have the extensive lymph node spread? Do you do like you do the roulette wheel and try and do a curative resection for that patient hoping it is ampullary?

Dr Aranha: We are very aggressive with all patients with cancer in the periampullary area that we feel are resectable. Therefore, we would do the same resection that we would do for an AC that we would do for a pancreatic cancer. We do a complete node dissection to include the celiac nodes but do not include periaortic node. Dr Pisters and his group will take up this question in the next article.

Peter W. T. Pisters, MD, Houston, Tex: Gerry, I enjoyed this paper immensely. I have 1 simple question. Do you have any data on the use of adjuvant therapy in your patients and any thoughts as to whether that may have influenced your estimates of event-free outcome for this patient population?

Dr Aranha: We have data, but we have not analyzed it. Our patients with AC who are node positive are treated in the same manner as those who have pancreatic carcinoma. We use size, status of lymph nodes, and other factors to give adjunctive therapy to patients with pancreatic carcinoma. These data are transposed to patients with AC.