PAPER

Improved Survival for Adenocarcinoma of the Ampulla of Vater

Fifty-five Consecutive Resections

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Hypothesis: After resection of an adenocarcinoma of the ampulla of Vater, certain clinical and pathologic characteristics influence long-term survival.

Design: Retrospective case series.

Setting: Major academic medical and pancreatic surgical center.

Patients: Fifty-five consecutive patients who underwent Whipple resection for ampullary adenocarcinoma from 1988 through 2001.

Interventions: Pylorus-preserving Whipple resection in 32 patients and standard Whipple resection in 23 patients.

Main Outcome Measures: Postoperative survival. A multivariate Cox proportional hazards model was used to determine the effects of various factors on long-term survival after resection.

Results: There were no operative deaths, and all patients left the hospital. After a mean follow-up of 46.9 months, the overall 5-year Kaplan-Meier survival estimate was 67.7%. The median survival of the entire group has not yet been reached. Five-year postoperative survival estimates for node-negative (n=32) and node-positive patients (n=23) were 76.5% and 53.4%, respectively (P=.26). Patients whose tumors demonstrated perineural invasion (n=12) had a 5-year survival estimate of 29.2% vs 78.8% for those whose did not (P<.001). On multivariate analysis, the absence of perineural invasion (P<.001) was an independent predictor of significantly improved postoperative survival.

Conclusions: Compared with previous reports from our own and other centers, this series demonstrates improved postoperative survival by 10% to 20% in patients undergoing Whipple resection for adenocarcinoma of the ampulla of Vater. The reasons for this improved outcome are unclear, and the effect of adjuvant treatment cannot be determined from this analysis. The major factor associated with prolonged survival was the absence of perineural invasion in the resected tumor specimen.

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ADENOCARCINOMA of the ampulla of Vater is a relatively uncommon tumor, as it accounts for less than 1% of all gastrointestinal malignancies.[1] However, it remains the second most common periampullary malignancy,[2,3] and at major pancreatic surgery centers in the United States, it accounts for up to 30% of Whipple resections performed.[1,4,5] The prognosis of this neoplasm is better than that of pancreatic cancer, with 5-year survival rates after resection between 30% and 60%.[1-20] Nevertheless, up to 60% of these patients will experience tumor recurrence and eventually die of their disease.[1,2,12,13]

In an attempt to identify characteristics predictive of postoperative survival and likelihood of disease recurrence, others have reviewed their experience with ampullary cancer.[1-4,10,14,17] Many of these studies, however, include cases operated on during multiple decades by many different surgeons with significant variations in surgical technique. Furthermore, some of the reports review operative outcomes of pancreatoduodenectomy at a time when the procedure carried with it a risk of substantially higher mortality than it does today.[2,11] During the last 2 decades, improvements in surgical and anesthetic techniques, critical care, and institutional specialization have decreased perioperative mortality rates of the Whipple resection to below 5% in most major centers.[21,22] In this report, we review an approximately 13-year experience with Whipple resection, both standard (SW) and pylorus-preserving (PPW)

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Table 1. Whipple Resections at University of California–Los Angeles Medical Center, 1988-2002

Primary Organ	All Resections	Standard	Pylorus-Preserving
Pancreas	**233** (64.7%)	83	150
Adenocarcinoma	132	58	74
Chronic pancreatitis	29	9	20
Benign cystic neoplasm	15	2	13
IPMN	15	1	14
Islet cell tumors	11	3	8
Mucinous cystadenocarcinoma	10	4	6
Neuroendocrine carcinoma	4	1	3
Adenoma	2	1	1
Carcinosarcoma	2	1	1
Adenosquamous carcinoma	1	1	0
Serous cystadenocarcinoma	1	0	1
Others	11	2	9
Ampulla of Vater	**74** (20.6%)	27	47
Adenocarcinoma	63	23	40
Adenoma	6	1	5
Lymphoma	1	1	0
Others	4	2	2
Duodenum	**28** (7.5%)	10	18
Adenocarcinoma	17	8	9
Adenoma	6	0	6
Sarcoma	2	1	1
Others	3	1	2
Bile duct	**24** (6.7%)	8	16
Adenocarcinoma	22	7	15
Atypia	2	1	1
Liver	1	0	1
Isolated HCC recurrence	1	0	1
Total	**360**	**128**	**232**

Abbreviations: HCC, hepatocellular carcinoma; IPMN, intraductal papillary mucinous neoplasm.

types, for adenocarcinoma of the ampulla of Vater at the University of California–Los Angeles (UCLA) Medical Center.

METHODS

DATA COLLECTION

We reviewed the medical records of 55 patients who underwent Whipple resection for adenocarcinoma of the ampulla of Vater at UCLA Medical Center between October 14, 1988, and July 24, 2001. Tumor origin was confirmed through microscopic histologic analysis, and only patients with ampullary adenocarcinoma were included. Patients with ampullary adenoma, ampullary fibrosis, adenosquamous carcinoma, carcinosarcoma, or other unusual tumors of the ampulla were excluded from this analysis. Follow-up data were obtained through medical record review, direct patient contact, and through United States Social Security record examinations. The review included patient demographics (age, sex, race, and date of diagnosis), symptoms on initial examination (jaundice, pain, gastrointestinal bleeding, and pancreatitis), surgical data (type of resection, operative blood loss, duration of surgery, transfusion requirement, and perioperative complications), tumor characteristics (size, degree of differentiation, depth of invasion, surgical margin status, perineural invasion, lymphovascular invasion, and lymph node involvement), and use of adjuvant chemotherapy and/or radiotherapy. For postoperative morbidity analysis, delayed gastric emptying was defined as intolerance to oral intake and need for nasogastric decompression following postoperative day 7, as well as slow transit of contrast from the stomach to the jejunal limb demonstrated on upper gastrointestinal radiographic contrast examination. In addition, a pancreatic fistula was defined as drainage of greater than 30 mL of amylase-rich fluid (at least 3 times the serum amylase concentration) from intraoperatively placed closed-suction drains after the fifth postoperative day.

SURGICAL TECHNIQUE

Forty-four (80%) of the 55 resections were performed by 1 surgeon (H.A.R.), so variations in technique in the collected series were minimal. Six other experienced pancreatic surgeons performed the remaining 11 resections. The operative approach for the Whipple resection has been described elsewhere.[23] It involved a standard lymph node dissection in all cases, which included clearance of the soft tissues and nodes along the right side of the superior mesenteric artery and anterior to the aorta. The pancreaticojejunostomy was performed as a 2-layer anastomosis, and pancreatic duct stents were not used. The hepaticojejunostomy was performed as a single-layer anastomosis. For SW, an antrectomy was performed. For PPW, the duodenum was transected 2 to 4 cm distal to the pylorus, and the right gastric artery was usually divided. Gastro(duodeno)-jejunostomy was performed in a retrocolic position in most cases. Closed-suction drains were placed near the biliary and pancreatic anastomoses, and a T-tube was used to stent the hepaticojejunostomy if the bile duct was less than 1 cm in diameter. Patients left the operating room with a nasogastric tube in place, which was removed the next morning.

STATISTICAL ANALYSIS

Data are presented as mean ± SD unless otherwise indicated. The effect of the type of operation on the incidence of specific postoperative complications was analyzed with the χ^2 test. Survival estimates were generated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. A multivariate Cox proportional hazards model was established to evaluate which factors independently affected postoperative survival. Selection of prognostic variables was intuitive and based on apparent clinical relevance. Statistical significance was achieved at $P<.05$. Statistical analyses were performed using SAS statistical software (SAS Institute, Cary, NC).

RESULTS

PATIENT CHARACTERISTICS

From October 1988, to January 1, 2003, 360 Whipple resections were performed at UCLA Medical Center for a variety of indications (**Table 1**). Most of these (118 [32.8%] of 360) were done for pancreatic adenocarcinoma. Sixty-two patients (17.2%) had resections for carcinoma of the ampulla of Vater. To provide sufficient follow-up time, our retrospective analysis was restricted to the period from October 1988 to August 2001, during which 55 patients underwent Whipple resection for ampullary cancer. The mean age at the time of surgery was 67.3 years (range, 28-87 years). Thirty-four of the patients (61.8%) were male, and 21 (38.2%) were female. Forty-five patients (81.8%) were white, 5 (9.1%) were Asian American, 3 (5.5%) were Hispanic, 1 (1.8%) was African American, and 1 (1.8%) was Filipino. Demographic data are presented in **Table 2**.

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The most common initial symptoms included jaundice (69%), abdominal pain (48%), and weight loss (38%). Eight patients (14.5%) were completely asymptomatic and had their periampullary lesions discovered on workups that had been initiated by abnormalities on routine serum liver function tests; 3 of these patients later developed jaundice during the course of the workup. Ninety-two percent of patients had a preoperative computed tomography scan, and 92% underwent endoscopic retrograde cholangiopancreatography as part of the diagnostic process. In only 12.5% of patients did computed tomography scans demonstrate a periampullary mass; however, a dilated biliary system was identified on 51.4% of computed tomography scans. Endoscopic retrograde cholangiopancreatography revealed a dilated biliary system in 40% of patients and an ampullary mass in 64.6% (fine-needle biopsy showed adenocarcinoma in 48.4% of the patients with masses). Twenty-five patients (45.5%) received preoperative biliary stenting with an endoprosthesis placed at the time of the endoscopic retrograde cholangiopancreatography.

OPERATIVE RESULTS

According to the preference of the operating surgeon, 23 patients (41.8%) underwent SW, while 32 (58.2%) underwent PPW (**Table 3**). The mean duration of all of the operations was 6.9±1.6 hours (SW, 7.98±1.7 hours; PPW, 6.1±0.9 hours). Thirteen patients (23.6%) received intraoperative blood transfusions, and the mean estimated blood loss at operation was 493 mL (range, 100-1700 mL). Intraoperatively, there were no deaths or complications. The mean length of hospital stay for all patients was 14.2±5.5 days (SW, 14.6±4.9 days; PPW, 14.0±6.0 days). Postoperatively, 20 patients (36.4%) spent time in the intensive care unit, but after May 1996, when the routine postoperative care pathway for Whipple resection was changed, only 2 (5.4%) of 37 patients actually required and received such monitoring. There were no perioperative deaths.

Postoperative complications occurred in 27 of the 55 patients, for an overall postoperative morbidity rate of 49.1%. Pancreatic fistula occurred in 12 (21.8%) of 55 patients, and delayed gastric emptying in 10 (18.2%) of 55 patients. Delayed gastric emptying associated with pancreatic fistula occurred in 3 patients; thus, in 3 (3%) of 10 patients with delayed gastric emptying and in 3 (25%) of 12 patients with pancreatic fistula, these 2 complications occurred together. Other complications included wound infection (10.9%), intra-abdominal fluid collection without evidence for anastomotic leak (5.5%), and urinary tract infection (1.8%). Postoperative complications occurred in 9 (39%) of 23 patients who underwent SW and in 18 (56%) of 32 patients who underwent PPW. In the 23 patients undergoing SW, 4 had pancreatic fistulas (17%), and 3 had delayed gastric emptying (13%). Of the 32 patients who had PPW, 7 had pancreatic fistulas (21.8%), and 7 had delayed gastric emptying (21.8%). Neither pancreatic fistula ($P=.5$) nor delayed gastric emptying ($P=.4$) was significantly more common in the PPW group vs the SW group (χ^2 test). Postoperative complications are presented in **Table 4**.

Table 2. Demographics of Patients Undergoing Whipple Resection for Adenocarcinoma of the Ampulla of Vater at UCLA, 1988-2001*

	All Patients (n = 55)	Standard (n = 23)	Pylorus-Preserving (n = 32)
Age, mean (range), y	67.3 (28-87)	67.3 (50-87)	67.3 (28-84)
Sex			
Male	34 (61.8)	14 (60.9)	20 (62.5)
Female	21 (38.2)	9 (39.1)	12 (37.5)
Race			
White	45 (81.8)	15 (65.2)	30 (93.8)
Asian	5 (9.1)	4 (17.4)	1 (3.1)
Hispanic	3 (5.5)	2 (8.8)	1 (3.1)
African American	1 (1.8)	1 (4.3)	0 (0.0)
Filipino	1 (1.8)	1 (4.3)	0 (0.0)

Abbreviation: UCLA, University of California–Los Angeles.
*Data are given as number (percentage) of patients.

Table 3. Intraoperative Data

	All Resections	Standard	Pylorus-Preserving
Mean time, h	6.9 ± 1.6	7.98 ± 1.7	6.1 ± 0.9
Blood loss, mean (range), mL	493 (100-1700)	697 (100-1200)	347 (100-1700)
Transfusions, units	0.4	0.9	0.06
Complications	0	0	0

Table 4. Perioperative Morbidity and Mortality

	No. (%) of Patients		
	All Resections (n = 55)	Standard (n = 23)	Pylorus-Preserving (n = 32)
Mortality	0	0	0
Overall morbidity	27 (49.1)	9 (39.1)	18 (56.3)
Pancreatic fistula	12 (21.8)	4 (17.4)	8 (25)
Delayed gastric emptying	10 (18.2)	3 (13.0)	7 (21.9)
Wound infection	6 (10.9)	2 (8.7)	4 (12.5)
Abdominal fluid collection	3 (5.5)	0	3 (9.4)
Deep venous thrombosis	2 (3.6)	0	2 (6.3)
Urinary tract infection	1 (1.8)	0	1 (3.1)
Pulmonary embolism	1 (1.8)	0	1 (3.1)
Pneumonia	1 (1.8)	0	1 (3.1)
Biliary stricture	1 (1.8)	0	1 (3.1)

TUMOR CHARACTERISTICS

A summary of pathologic characteristics of resected tumors can be found in **Table 5**. The mean size of the tumors was 1.93 cm in maximal diameter (range, 0.4-6.5 cm). All specimens contained invasive adenocarcinoma originating from the ampulla of Vater. Three tumors were noted to have mucinous features, 1 adenocarcinoma had arisen in a villous adenoma, and 1 contained signet-ring cells. Eleven tumors (20%) were well-differentiated, 33

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Table 5. Tumor Characteristics

Total No. of specimens	55
Adenocarcinoma	55
Size, mean (range), cm	1.93 (0.5-6.5)
Grade	
Well-differentiated	11 (20)
Moderately differentiated	33 (60)
Poorly differentiated	11 (20)
Margins	
Positive	1 (1.8)
Negative	54 (98.2)
Depth of invasion	
Limited by muscularis mucosae	4 (7.3)
Into submucosa	9 (16.4)
Into muscularis propria	17 (30.9)
Full thickness (into adjacent pancreas)	23 (41.8)
Undetermined	2 (3.6)
Microscopic features	
Lymphovascular invasion	9 (16.4)
Perineural invasion	12 (21.8)
Regional lymph nodes	
Lymph node metastasis	23 (41.8)
No lymph node metastasis	32 (58.2)

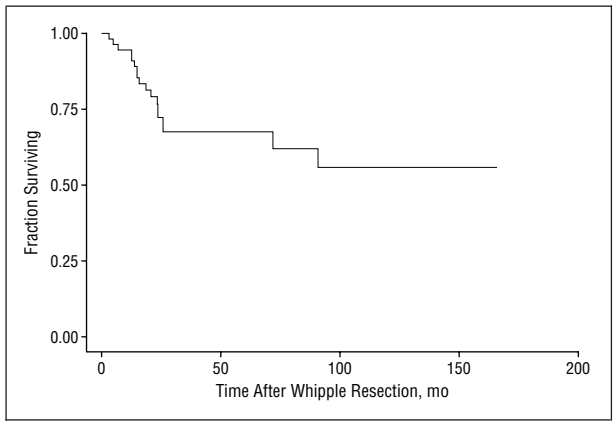

Figure 1. Kaplan-Meier survival estimate after Whipple resection for ampullary adenocarcinoma. The 5-year postoperative actuarial survival rate for the entire cohort of 55 patients was 67.7%, and the median survival had not been reached.

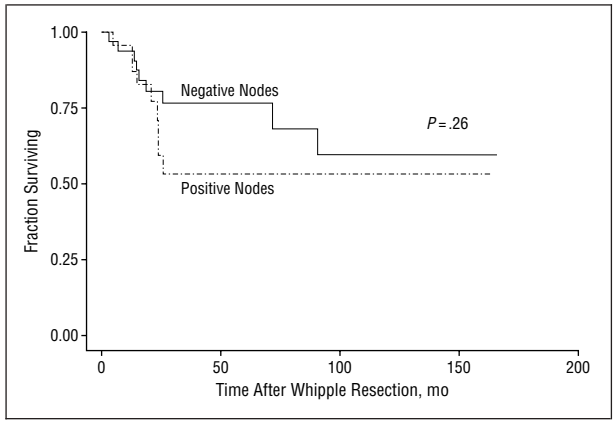

Figure 2. Kaplan-Meier survival estimate after Whipple resection for ampullary adenocarcinoma and the influence of nodal status. Nodal status did not significantly influence survival, as patients with node-negative resections had a 5-year actuarial survival rate of 76.5% vs 53.4% for those with lymph node metastases (P=.26, log-rank test).

(60%) were moderately differentiated, and 11 (20%) were poorly differentiated. One tumor demonstrated microscopic invasive adenocarcinoma at the resection margin where the primary tumor was adherent to the superior mesenteric vein, and the positive margin was the wall of a tributary of that vein. The vein was not resected because the surgeon also detected invasion into the tissues adjacent to the superior mesenteric artery, as well. The bile duct, duodenal, and pancreatic margins were all free of carcinoma. This patient died 4 months following surgery.

On microscopic examination, 12 tumors (21.8%) had perineural invasion, 9 (16.4%) had lymphovascular invasion, and 23 (41.8%) had lymph node metastases. Thirty-two patients (58.2%) had node-negative resections. Those patients with lymph node involvement had a mean of 1.0 positive nodes per specimen (range, 1-8 nodes) and a mean of 8.9 nodes were examined microscopically per specimen (range, 1-35 nodes). Forty-three percent of patients who underwent SW had positive lymph nodes (mean, 9.8 nodes examined per specimen), whereas 40.6% had positive nodes on PPW (mean, 8.3 nodes examined per specimen; P=.5). Twenty-three tumors (41.8%) showed full-thickness invasion through the ampulla to adjacent tissues (ie, pancreas); 17 (30.9%) invaded into, but not through, the muscularis propria; 9 (16.4%) invaded the submucosa; 4 (5.5%) had invasive tumor confined to the mucosa; and 2 (3.6%) had undetermined depths of invasion. According to the 6th edition of the *American Joint Committee on Cancer Staging Manual*,[24] 4 patients (7.3%) had stage 0 disease (confined to the mucosa overlying the ampulla), 17 (30.9%) had stage IB (invading the duodenal wall but no nodal involvement), 10 (18.2%) had stage IIA (invading the pancreas but no nodal involvement), and 23 (41.8%) had stage IIB (regional nodal metastases present). One patient (1.8%) could not be adequately staged (nodes were negative, but the depth of tumor invasion was undetermined).

SURVIVAL OUTCOMES

All patients had at least 1 year of follow-up, and 52 (94.5%) of 55 survived 1 year after surgery. At a mean follow-up of 46.9 months, 37 (67.3%) of the 55 patients were alive. Twenty-four (61.5%) of 39 patients were alive at 3 years, and 16 (61.5%) of 26 patients were alive at 5 years postresection. Thus far, 5 patients (9.1%) have survived at least 125 months, 10 (18.2%) at least 80 months, 14 (25.5%) at least 60 months, 24 (43.6%) at least 36 months, and 34 (61.8%) at least 24 months after surgery. The overall 5-year postoperative Kaplan-Meier survival estimate for all 55 patients was 67.7% (**Figure 1**), and the median survival for this group of patients has not yet been reached. Patients with node-negative resections had improved 5-year survival estimates compared with those with positive nodes (76.5% vs 53.4%, respectively), but this difference did not reach significance on univariate analysis (P=.26, log-rank test) (**Figure 2**). Patients with evidence of perineural invasion had a significantly poorer 5-year survival estimate compared with those without perineural invasion (29.2% vs 78.8%, respectively, P<.001, log rank test) (**Figure 3**). Well-differentiated

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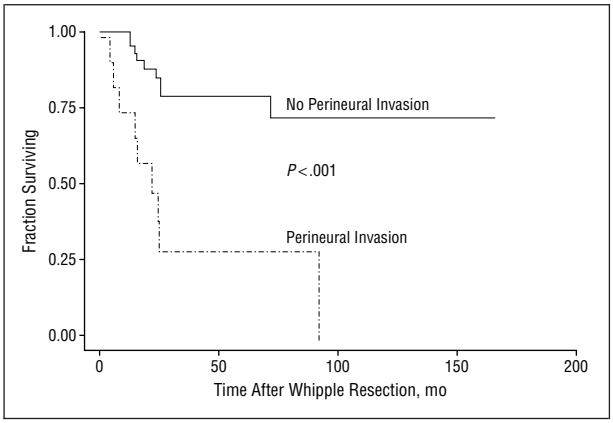

Figure 3. Kaplan-Meier survival estimate after Whipple resection for ampullary adenocarcinoma and the influence of perineural invasion. Perineural invasion was indicative of a significantly poorer prognosis after resection: 78.8% 5-year actuarial survival for those without perineural invasion vs 29.2% for those with perineural invasion ($P<.001$, log-rank test).

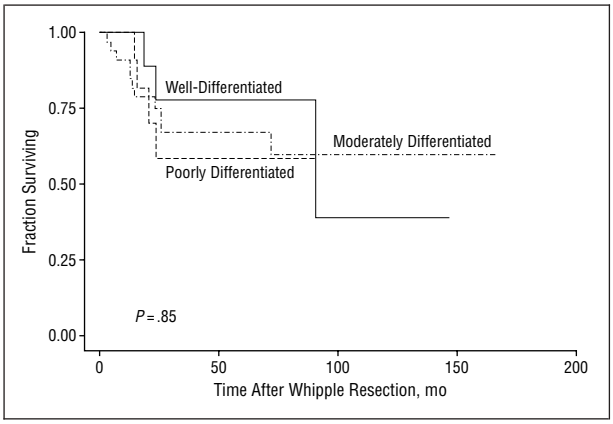

Figure 4. Survival estimate after Whipple resection for ampullary adenocarcinoma and the influence of tumor grade. The 5-year actuarial survival rates according to tumor grade were as follows: well-differentiated, 77.8%; moderately differentiated, 67.1%; and poorly differentiated, 58.4%. There was no significant difference between survival rates for well-differentiated vs poorly differentiated tumors ($P=.85$, log-rank test).

tumors had an improved 5-year survival estimate (77.8%) compared with poorly differentiated tumors (58.4%), but this difference did not reach significance ($P=.85$, log-rank test) (**Figure 4**). Examination of Kaplan-Meier survival estimates according to the type of resection demonstrated 1- and 5-year rates of 90.6% and 67.7%, respectively, for PPW, and 91.3% and 65.2% for SW. These survival rates did not differ significantly between the SW and the PPW groups ($P=.73$, log-rank test) (**Figure 5**). Twenty-six patients received adjuvant treatment following postoperative recovery. For this group of patients, 1-, 2-, and 5-year survival estimates were 89.5%, 49.8%, and 37.3%, respectively. It was of interest that all of the survival curves appeared to flatten after about 2 years of follow-up. Thus, patients surviving 2 years after resection had an 88.1% chance of living an additional 3 years, and an 80.7% chance of living an additional 5 years (Kaplan-Meier estimate).

In a multivariate Cox proportional hazards model (**Table 6**), the presence of perineural invasion (hazard ratio 20.1, $P<.001$) was identified as a predictor of significantly worse postoperative survival. Age, tumor size, lymph node status, type of resection, and depth of tumor invasion did not independently affect long-term survival. In addition, a positive resection margin (hazard ratio, 47.1; $P=.003$) also appeared to independently affect postoperative survival; however, this statistic possesses little more than observational value, as only 1 of 55 patients had a positive margin. Therefore, resection margin status is not considered to be an independent prognostic factor in this analysis.

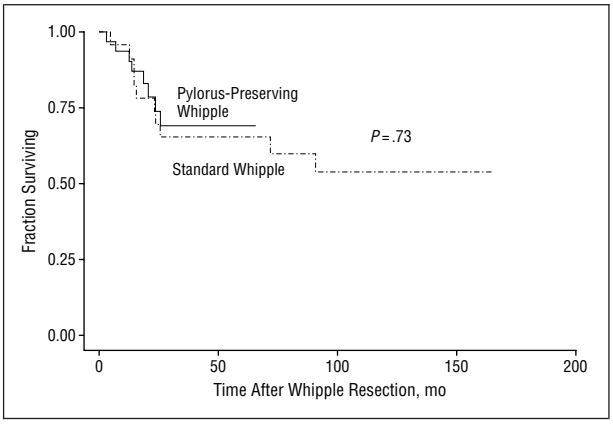

Figure 5. Actuarial survival after Whipple resection for ampullary adenocarcinoma and the influence of resection type. Five-year actuarial survival was similar for standard Whipple resection compared with the pylorus-preserving type (65.2% vs 67.7%, respectively; $P=.73$).

Table 6. Multivariate Analysis of Prognostic Factors for Ampullary Adenocarcinoma Following Whipple Resection

Factor	Hazard Ratio	*P* Value*
Perineural invasion	20.151	<.001
Tumor size	1.416	.13
Patient age	1.029	.3
Type of operation (SW vs PPW)	0.613	.4
Depth of invasion	0.967	.93
Lymph node status	0.971	.98

Abbreviations: PPW, pylorus-preserving Whipple resection; SW, standard Whipple resection.
*Cox proportional hazards model.

COMMENT

The first successful en bloc pancreatoduodenal resection for ampullary adenocarcinoma in the US was reported by Whipple and colleagues in 1935.[25] Two years following this 2-stage operation, the patient died with hepatic metastases.[26] Since that time, numerous studies have examined the outcomes of Whipple resection for ampullary cancer.[1-20,27-29] All of these reports are retrospective case series, many have limited case numbers, only 1 is multi-institutional,[29] and only a limited number of recent studies focus on outcomes during the last 2 decades.[5,15,17-20,27,28,30] Of the largest single-institution reviews of ampullary adenocarcinoma to date—from the Lahey Clinic (112 patients, 1942-1971), the Mayo Clinic (74 patients, 1965-1989), the Johns Hopkins Hospital (120 patients, 1969-1996), and the Memorial Sloan-

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Kettering Cancer Center (123 patients, 1983-1995)—only the one from Memorial Sloan-Kettering (as well as more recent reviews of all periampullary cancers at Johns Hopkins) examines a primarily contemporary experience.[1,2,6,7,30] As a result, in most of these reports, survival data may be adversely affected by the higher perioperative morbidity and mortality rates encountered during these periods.

Therefore, despite its relatively small size (55 patients), the present study benefits from its focus on recent survival outcomes during the last 15 years. This is a period that is characterized by significant advances in imaging technology, surgical technique, anesthesia, critical care, interventional radiology, and regionalization of such procedures to major pancreatic surgery centers. Because most of our patients also were treated by a single surgeon, the current analysis also may more accurately reflect the clinical outcome to be expected from current-day treatment.

Previous studies have demonstrated that survival after resection for ampullary carcinoma is better than that for pancreatic cancer. Overall 5-year survival rates in these reports have ranged from 20% to 61% (mean, 43.4%), compared with 17% to 20% for pancreatic cancer.[1-20,27-29] Previous studies have also shown that patients undergoing resection have significantly longer survival compared with those who receive palliative care alone.[1,2,10,15] Although this seems intuitively apparent, we cannot make such an analysis here since we did not review a comparable group of patients who were not resected. Nevertheless, in the present study, overall 5-year postoperative survival was 67.7%, compared with rates of 20% to 61% reported previously.[1-20] This represents an impressive increase in 5-year survival rates over historical controls[1-20] and is consistent with the more recent observations of improved survival following resection for pancreatic cancer, as well. A recent study from Johns Hopkins designed to test the possible benefit of a more extensive lymphadenectomy in patients with pancreatic and other periampullary tumors included 62 patients with ampullary cancers.[26] Five-year survival estimates were similar for the standard lymphadenectomy (56%) and the radical groups (60%). In the present study, all of the patients had a standard lymphadenectomy.

The factors responsible for this improvement are not immediately obvious. The recent time frame of our series suggests that our patients might have benefited from improved diagnostic techniques (eg, helical computed tomographic scan, endoscopic ultrasound), resulting in earlier diagnosis and increased resectability, but we have no direct evidence to support this. It is of note that 8 (14.5%) of 55 of our patients were completely asymptomatic and had their diagnostic workups initiated solely by abnormal serum liver enzymes. This observation raises the possibility that our patients had less advanced disease than those described in other series that do not describe asymptomatic presentations.[2,10] However, 4 of these 8 had lymph node metastases (stage IIB), and the other 4 had disease invading the duodenal wall (stage IA). Analysis of all specimens in our series revealed that 23 (41.8%) had lymph node metastases (stage IIB), and 40 (72.7%) had tumor penetration at least into the duodenal wall, with 23 (41.8%) of these infiltrating the pancreas. These numbers fall within the ranges established by previous series for lymph node involvement (28%-55%; references 1, 2, 4, 9, 12) and for local invasion of the duodenum and pancreas (72%-86%; references 1 and 4). Thus, although 15% of our patients were asymptomatic at the time of diagnosis, our series includes tumors with invasive and metastatic properties similar to those from other reports.

Theoretically, patient survival could also have been extended by adjuvant treatment with newer chemotherapeutic agents. Although 26 individuals had adjuvant treatment, these patients actually had survival rates lower than those of the entire cohort (5-year survival, 37.3% vs 67.7%, respectively). The reason for this may be that the patients who received adjuvant therapy also had the most "unfavorable" tumor characteristics: full-thickness invasion into the pancreas (75%), lymph node metastases (78%), perineural invasion (33%), and moderate or poor degree of tumor differentiation (89%). We caution that it is not possible to draw any conclusions about the role of adjuvant therapy from this analysis, however. There was no standard protocol to decide which patients were treated, and those who were treated did not all receive the same drug(s); some also received radiation. Further study is needed in this area.

Various clinicopathologic factors have been found to favorably influence long-term survival after Whipple resection for ampullary and periampullary cancers. Among them are absence of intraoperative transfusion,[2,5] absence of microscopic lymph node involvement,[1,2,5,13,19] well-differentiated tumors,[2,5,10,13] small tumor size,[14] absence of tumor at resection margins,[1,3,5] absence of perineural invasion,[4] confinement of tumor to the ampulla vs invasion into the pancreas,[4] and use of adjuvant chemotherapy.[4] In our series, the absence of perineural invasion predicted significantly improved postoperative survival. Whereas perineural invasion has frequently been recognized as a characteristic feature and indicator of poor prognosis in pancreatic cancer,[31] its importance in other gastrointestinal tumors is less well described. Our series reinforces the findings of Chan et al[4] and Yamaguchi and Nishihara[32] that perineural invasion portends poor prognosis for patients with ampullary adenocarcinoma. In our study, the 12 patients with perineural invasion had a risk of dying that was more than 20 times that of patients without it. Continued clinical and basic science investigation is ongoing to elucidate the molecular mechanisms underlying the significance of this observation.

The importance of achieving clean margins in an oncologic resection is intuitively apparent, and we routinely perform frozen section microscopic analysis of the bile duct, gastro(duodenal), and pancreatic margins. Any evidence for cancer dictates further resection along the affected margin, and microscopic reexamination. This protocol likely accounts for the low numbers of reported positive resection margins at other centers as well as ours.[30] The single patient with a positive resection margin had carcinoma that invaded the wall of a tributary of the superior mesenteric vein, and gross evidence that the cancer had also extended to the superior mesenteric artery. Thus, the superior mesenteric vein/portal vein was not resected in this patient, since it was apparent that this

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would not have removed all of the tumor. Multivariate analysis indicated that the presence of this positive margin significantly influenced survival; however, as it only occurred in a single patient, this observation has no statistical validity. Thus, although resection margin status has been shown to be a significant prognostic factor in other series on ampullary cancer, as well as in a variety of gastrointestinal malignancies,[1,3,5] we cannot make such a claim based on our analysis.

The type of resection (SW vs PPW) did not independently influence survival. Analysis of the pathology reports revealed that similar numbers of nodes were examined (8.3 in PPW vs 9.8 in SW), and that there were similar numbers of patients with lymph node involvement (40% in PPW vs 43% in SW). These results for ampullary adenocarcinoma strengthen the notion that, with appropriate technique, the PPW is oncologically equivalent to the SW. While our patients with nodal metastases had lower 5-year survival rates than those with node-negative resections (53.4% vs 76.5%), lymph node involvement was not a significant prognostic indicator by univariate analysis ($P=.26$, log-rank test). This is in contrast with several studies that demonstrate the prognostic significance of lymph node metastasis in ampullary cancers.[1,2,5,13,19] Forty-two percent of our patients had lymph node metastases, which is similar to findings in other series, where 39% to 45% of specimens had nodal involvement.[1,2,27,30] Although 1 surgeon performed 80% of the resections with identical technique, great variability existed in the number of nodes identified and examined by the pathologists for each specimen (range, 1-35 nodes). This variability in the completeness of examination of the removed nodes, as well as our relatively small sample size (n=55), may explain why lymph node status was not an independent predictor of postoperative survival in this series.

Despite the improved 5-year survival rate and absence of perioperative mortality in our patients, postoperative morbidity continued to pose a major surgical challenge. Complications occurred in nearly half (49.1%) of our patients. Delayed gastric emptying (18.2%) and pancreatic fistula (21.8%) were the most prominent. Although delayed gastric emptying occurred more commonly in patients who underwent PPW (21.8% PPW vs 14% SW), the difference was not statistically significant ($P=.4$). This is similar to our experience with delayed emptying when the Whipple resection is performed for other indications, eg, incidence of delayed gastric emptying in the last 360 consecutive Whipple resections: 16% of PPW patients, and 11% of SW patients [$P=.2$]). The rate of pancreatic fistula in our patients (21.8%) was higher than the 1% to 14% rate reported for the same operation for pancreatic cancer[30,33-34] but similar to the 22% to 25% reported after Whipple resection for ampullary cancers from other centers.[2,9,10,30] In the current study, there was no significant difference in the incidence of pancreatic fistula after SW (17.4%) vs PPW (25%) ($P=.5$). At UCLA during the same period as this review, our pancreatic fistula rate in more than 130 Whipple resections for pancreatic cancer was 6%. The increased fistula rate in the ampullary cancer patients is almost certainly the result of the soft pancreatic tissue found in most of them. Although the tumors frequently produce some element of pancreatic and bile duct obstruction, the same degree of pancreatic fibrosis as is typically found with pancreatic cancers does not generally develop. In some of these patients, octreotide was given in the postoperative period to try to minimize the development of this complication; however, we have not used it routinely.[35,36] Nevertheless, with today's closed-suction drains and with expertise in interventional radiology, a pancreatic fistula rarely becomes clinically significant. No patients with pancreatic fistula in this cohort experienced sepsis or any other related problem, and the presence of fistula did not increase the duration of hospital stay. Most fistulas closed within 2 weeks of discharge, and the drains were removed in the office at the first postoperative visit.

Some surgeons advocate local resection for small ampullary tumors with certain favorable features.[37] We agree that benign lesions that do not appear to invade the muscular layers of the duodenum when studied by endoscopic ultrasound may be locally resected. Nevertheless, every lesion removed that way should be assessed by frozen section examination during the operation, and a Whipple resection should be performed for medically fit patients who have invasive carcinoma. As is apparent, the operation can be done safely with very low mortality rates and impressive long-term survival.

In summary, the experience with Whipple resection for adenocarcinoma of the ampulla of Vater at UCLA Medical Center during the last 15 years demonstrates improved postoperative survival by 10% to 20% compared with historical controls. The major factor predicting increased survival after resection was the absence of perineural invasion by tumor cells. While patients with lymph node involvement had decreased postoperative survival, lymph node status was not a predictive factor of poorer prognosis on multivariate analysis. Whipple resection for ampullary adenocarcinoma can be performed with minimal perioperative mortality rates, and although postoperative complications are common, they usually are not serious. While local resection may be appropriate for some patients with ampullary tumors that meet strict criteria, Whipple resection continues to be the procedure of choice for ampullary adenocarcinoma.

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DISCUSSION

Clifford W. Deveney, MD, Portland, Ore: The authors recount their experience with pancreaticoduodenectomy in the treatment of carcinoma of the ampulla of Vater. Over a period of 13 years, from 1988 to 2001, the authors performed pancreaticoduodenectomy on 55 patients for ampullary carcinoma. The series is exemplary for the absence of any deaths. Only 23% of patients required blood transfusion, and the average blood loss was less than 500 mL. These results compare quite favorably with other recent reports of the Whipple operation and should be used as a standard.

Thirty-two (58%) of the patients had a pylorus-preserving Whipple operation, while the other patients had the standard Whipple procedure. Delayed gastric emptying occurred in 18% of patients and did not differ between the standard or pylorus-preserving Whipple procedure.

Pancreatic fistula occurred in 22%, and the incidence of this complication also did not differ between the procedures. Follow-up on these patients was a minimum of 1 year on all patients. Three-year survival was 62%, and actuarial 5-year survival was 68%. Thus, a 2- to 3-year survival was indicative of cure. Perineural involvement as well as positive margins were the only independent variables associated with increased recurrence and death secondary to tumor. Tumor size and depth of invasion did not influence survival. Although those patients with poorly differentiated tumors and those with lymph node involvement had a poorer survival, these numbers did not achieve significance. This is an exemplary paper both in terms of operative mortality and morbidity as well as long-term survival, which approaches 70%.

I have 3 questions on which I would like the authors to comment. (1) What made you choose the standard over the pylorus-preserving Whipple? Most of these procedures were done by 1 surgeon, and perhaps you can comment on how you made the choice of doing one or the other procedure. (2) How did you make the diagnosis of delayed gastric emptying in your patients? Was this a clinical diagnosis or confirmed with any radiological or cinegraphic studies? (3) Would you comment on the improved long-term survival of your patients in terms of (a) improvements in operative technique, (b) earlier identification of tumor, and (c) more precise histologic diagnosis of the tumor? This paper will serve as a standard for treatment of that lesion, carcinoma of the ampulla of Vater.

Karen Deveney, MD, Portland: Other than those factors such as excellent operative technique, do you think that there were other factors causing the excellent results, such as what kind of adjuvant therapy did these patients with positive lymph nodes receive?

Theodore X. O'Connell, MD, Los Angeles, Calif: Is the change in survival due to (1) a change in tumor biology, (2) earlier diagnosis and stage, or (3) adjuvant treatment? What is making the impact on improved survival? The second com-

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ment is one about β errors in your statistics. When you have a β error, just because you can't prove things are statistically different, that's not saying they are the same. Since in his series there are small numbers, you may state that items are not statistically different, but you cannot say they are statistically the same. That problem is magnified, especially when you split the group into pyloric-sparing and standard Whipple. Delayed gastric emptying occurs in 13% of the standard Whipples and in about 22% of the pyloric sparing. Obviously, there is a difference of almost two-fold. It may not reach statistical difference because of the small numbers, but there is certainly a clinical difference. There may be a similar problem with tumor size impact on survival. So when you have such small numbers, you have a risk of saying, "these are not different statistically," but you can't say that they are "statistically the same" either.

Sean J. Mulvihill, MD, Salt Lake City, Utah: These are among the best results reported for this operation in the literature today. I have 2 questions. One relates to the role of local excision, which in our experience has been a useful technique for selected patients with small ampullary tumors, and I wonder if the authors would comment on their philosophy regarding its use.

The second question relates to the 3 major perioperative complications of delayed gastric emptying, pancreatic fistula, and wound infection. The rates of these complications in this group of patients are high relative to other types of operations that we do. I wonder if the authors could expand on their approach to reduce these complications.

Andrew Warshaw, MD, Boston, Mass: There are fine results reported here, perhaps improved over previous eras. I do have some questions about your analysis of data. Although your cure rates are much higher than those for pancreatic adenocarcinoma, marked perineural invasion was a marker of bad disease. Can you inform us about any molecular genetic differences that can account for this difference in behavior? Incidentally, the margin was positive in only 1 case, so I would caution against a β error in your statistics: you cannot really state a significant difference related to margins.

The next question has to do with your patient selection and definition of ampullary tumors. These, as you know, very often arise from villous adenomas of the ampulla that characteristically have a long history of indolence and benign histology before developing into invasive carcinoma. In your series, only 69% of your patients were jaundiced; 15% were asymptomatic; a mass was identified in only 65% on ERC (endoscopic retrograde cholangiography), and biopsy was positive for cancer in only 50% of the entire series. Do these findings imply that many had only carcinoma in situ or focally invasive carcinoma in a bed of villous adenoma? What was the total population from which your resected patients for the Whipple or pyloric-preserving pancreaticoduodenectomy were chosen? How many got an ampullectomy or could have gotten a local resection? If the biopsies were negative for cancer in half of your series, why didn't you do a local resection? Why did you choose to do the pancreaticoduodenectomy in those cases?

Why did the standard Whipple take 2 hours longer than a pylorus-preserving operation? In our experience, there is only about 20 minutes difference between the 2 techniques of operation. Was patient selection for more advanced tumors the basis for the difference? That hypothesis might be supported by the fact that blood loss and blood transfusion rates were higher in the Whipple subgroup.

L. William Traverso, MD, Seattle, Wash: This paper represents a milestone for which gastrointestinal surgeons throughout the country can be very proud because of the improved results. All of us who do these complex operations in this country are very proud to see these results that support what we do. I would like to ask 2 questions. The medical oncology input into this—are they part of the team with these patients? I would like to hear some more about that because UCLA has a great medical oncologist, Bill Isacoff. Can you give us some details about the impact of the chemoradiotherapy? How many of your patients had adjuvant chemotherapy protocols at UCLA?

Another part of the team is the pathologist. A pathologist has to be brought into this in a prospective way. The surgeon cuts the Whipple specimen in 5 places but there are multiple other surfaces that have to be examined for extension of tumor. When Dr Duffy did his review, I am sure he had trouble figuring out where the positive margins were by reviewing the pathologist's report. I am wondering if they could comment on how confusing it was since this was done retrospectively and whether they now have a prospective approach with the pathologist to look at these tumors? More subsets, other than perineural invasion, could really be examined to see if they make some importance there.

Dr Reber: A number of people raised questions about several similar problems, and I would like to try to address some of those issues all together. There were several who wondered about how the decision was made to do a standard Whipple operation or a pylorus-preserving Whipple. In the earlier years of this study, many of the surgeons at UCLA were a bit uncomfortable with the pylorus-preserving Whipple as an appropriate operation for a malignant neoplasm, and so there tended to be more standard Whipples done. As time went on, pylorus-preserving Whipple became more favored, and probably 99% of the operations that I do now are of the pylorus-preserving variety. So, the short answer to that question is that it was surgeon preference and really nothing more.

A number of questions related to the complications that occurred: delayed gastric emptying, in about 17%; pancreatic fistula, in about 22%; and wound infection, in about 10% of cases. The incidence of delayed gastric emptying and whether or not it is more frequent after pylorus-preserving operation continues to be debated around the world. I know that Dr Warshaw and his group don't do pylorus-preserving operations, generally speaking, because of their concern that the delayed emptying rate is too high. They are happier with the standard Whipple because they think that the frequency of delayed emptying is much lower. That's not accepted around the world without some debate, however. The Hopkins group and we at UCLA believe that there is no statistically significant difference. It is true that in the 55 patients that were presented today, and this relates as well to the β error issue that was brought up by several discussants, that the numbers of patients in the 2 groups are relatively small and it may be inappropriate to draw the conclusion that there is no difference. On the other hand, we have looked at about the last 400 Whipples done at UCLA and examined the frequency of delayed gastric emptying after the 2 operations. The incidence is in the neighborhood of 15% to 17% in each, and there is still no statistically significant difference, now with much larger numbers.

As far as pancreatic fistula is concerned, a couple of comments are in order. Yes, a higher rate than one might have expected, but this has been the frequency seen by others who have quite a bit of experience in the area. For example, the Hopkins group who reviewed their data after resections for ampullary cancer found that their incidence of pancreatic fistula after the Whipple operation was about 25%. So this is certainly in the same ballpark and we believe that the frequency of pancreatic fistula is as high as it is because the pancreas generally tends to be normal in consistency, soft, and doesn't hold sutures particularly well. Again, bringing it back to a comparison with the rest of the Whipple resections done in the UCLA experience, when we have done Whipple resections only for pancreatic cancer, our pancreatic fistula rate is 6%, which again is similar to the experience in other centers. So I think that it really does relate to the texture of the gland.

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Wound infection: I don't really have a good explanation for the rate of 10%. The only thing that occurs to me is that almost every one of these patients has biliary stents in place, and there are retrospective studies that suggest that once you introduce organisms into the bile by the placement of a stent into the common duct, the incidence of a variety of perioperative infections increases.

There were some questions about why, in the absence of any obvious explanation, these patients are doing so well, and are surviving longer than reports from many other series suggest, and certainly longer than patients with pancreatic cancer. Many people have suggested the possibility that patients with ampullary cancers are diagnosed earlier, and so the resection is done sooner, and as a result the disease has not spread to the same extent as in someone with a pancreatic neoplasm. That may be part of it, but I think that is unlikely to be the real answer. That there has to be a significant difference in the underlying biology of the tumor, and there are a variety of reasons to support that idea. For example various molecular markers suggest that the diseases are different. K-ras, as you know, is abnormal in at least 90% of patients with pancreatic cancer. It probably only is abnormal in about half of the patients with ampullary cancers. Perhaps 3 quarters of the ampullary cancers have been described as having an intestinal-type morphology histologically, and in only about a quarter do they appear morphologically like the typical pancreatic cancers. This suggests an underlying difference in growth patterns and probably biologic invasiveness. Ampullary cancers are known to occur with somewhat higher incidence in patients with familiar adenomatous polyposis. That is not the case with pancreatic cancer. On the other hand, with pancreatic cancer, there is an increased incidence with HNPCC (hereditary nonpolyposis colorectal cancer), with the FAM syndrome, and with Peutz-Jeghers syndrome. So there are many reasons to suspect that there really is an inherent difference in the basic biology of these 2 lesions, and I suspect that that has more to do with the better survival in ampullary cancer than any other data that are currently available.

Dr Warshaw asked the question about how many patients really had small tumors, and therefore might have been reasonably treated with local resection? You have seen, as presented by Dr Duffy, that the mean diameter of the tumors was about 2 cm. Virtually no one had a tumor that we would reasonably have considered removing with a local excision. In the occasional patient with very small tumors that appear on repeated biopsies to be benign, lesions that appear with endoscopic ultrasound examination to be limited to the mucosa, we have begun with a local resection. But at the time of the operation we await a frozen section analysis and if any of these are shown to contain invasive adenocarcinoma, the appropriate operation is a Whipple resection. None of the patients in this series started off with a local resection and then went on to a Whipple resection, however.

CME Announcement

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We apologize for the interruption in CME and hope that you will enjoy the improved online features that will be available in fall 2003.

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