ANNALS OF SURGERY
Vol. 228, No. 1, 87–94

Factors Predictive of Survival in Ampullary Carcinoma

James R. Howe, MD,* David S. Klimstra, MD,† Roger D. Moccia, BA,‡ Kevin C. Conlon, MD,‡ and Murray F. Brennan, MD‡

From the Division of Surgical Oncology, University of Iowa Hospitals and Clinics, and the Departments of Pathology† and Surgery,‡ Memorial Sloan-Kettering Cancer Center, New York, New York*

Objective

To review the recent Memorial Sloan-Kettering Cancer Center experience with adenocarcinoma of the ampulla of Vater and to identify clinicopathologic factors that have an impact on patient survival.

Summary Background Data

The prognosis for patients with tumors of the ampulla of Vater is improved relative to other periampullary neoplasms. Identification of independent prognostic factors in ampullary tumors has been limited by small numbers of tumors and a lack of pathologic review.

Methods

Data were collected prospectively for patients presenting with periampullary carcinomas to the Memorial Sloan-Kettering Cancer Center between October 15, 1983 and June 30, 1995. The correlation between clinicopathologic variables and survival of ampullary carcinoma was tested by the Kaplan-Meier method and log-rank test, and Cox proportional hazards regression. Survival of patients with periampullary adenocarcinomas was compared by the Kaplan-Meier method.

Results

In 123 patients presenting with ampullary carcinoma, 101 tumors (82.1%) were resected. Factors significantly correlated with improved survival were resection ($p < 0.01$), and in resected tumors, negative nodes ($p = 0.04$) and margins ($p = 0.02$) independently predicted for improved survival. In periampullary tumors, the highest rates of resection and overall survival (median, 43.6 months) were found in ampullary carcinomas.

Conclusions

Factors predictive of improved survival in ampullary carcinoma include resection, negative margins, and negative nodes. Improved overall survival in ampullary relative to periampullary adenocarcinoma is due in part to a significantly higher rate of resection.

The first radical resection for carcinoma of the ampulla of Vater was performed by Halsted in 1898, who resected part of the duodenum and reimplantated the common bile duct and pancreatic duct in the duodenum.[1] Unfortunately, this patient died 7 months later from a recurrent tumor. Although partial duodenectomy with removal of a portion of the head of the pancreas had been described by several other surgeons subsequently for ampullary tumors,[2] Whipple was the first to perform en bloc removal of the entire duodenum with the head of the pancreas in 1935.[3] This patient survived 25 months before dying of liver metastases.[4] Brunschwig was the first to perform this procedure for carcinoma of the head of the pancreas in 1937.[5] This operation was later refined to a one-stage procedure in 1940 by Whipple[6] and Trimble,[7] ushering in a new era for the effective surgical treatment of periampullary tumors.

Carcinoma of the ampulla of Vater is a relatively uncommon neoplasm, which accounts for approximately 6% of periampullary tumors,[8] with an incidence of approximately 5.7 cases per million population per year.[9] Surgical series of periampullary tumors have demonstrated that patients with ampullary tumors have a more favorable prognosis than those with pancreatic or bile duct tumors,[10–18] with median survivals of 30 to 50 months,[19,20] and 5-year survival rates

Address correspondence and reprint requests to Murray F. Brennan, Chairman, Department of Surgery, Room C-1265, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

Presented at the 50th Annual Cancer Symposium of The Society of Surgical Oncology, Chicago, Illinois, March 20–23, 1997.

Support for this project was provided by the Bernice and Milton Stern Foundation.

between 30% and 50%[21,22] in resected patients. In his musings on the evolution of panctreaticoduodenectomy, Whipple hypothesized several reasons for the improved prognosis of ampullary *versus* pancreatic tumors. He stated that "cancer of the pancreas is usually of the infiltrating, invasive, poorly differentiated type of growth; the cancer cells invade the lymphatic and blood vessels and nerves early. Furthermore, the pancreatic tumors do not cause an early jaundice, as do carcinomas of the ampulla or bile duct. The ampullary growths are usually of the fungating variety, the better differentiated of the adenomatous type, slower to invade the lymphatics and blood vessels."[4]

Studies attempting to confirm these hypotheses or to define important prognostic variables for patients with adenocarcinoma of the ampulla of Vater have been limited in several ways. Most have had only limited numbers of patients, usually operated on over several decades. Many have not performed multivariate analyses to identify independent prognostic factors, and the significance of different clinicopathologic factors has varied in the larger series. Perhaps the most significant problem with these studies is the lack of histologic review to confirm that tumors originate from the ampulla of Vater. Accidental inclusion of tumors of the pancreas, bile duct, or duodenum could dramatically alter the results of survival analyses. The main objective of this study was to determine the clinicopathologic factors predictive of survival in ampullary carcinoma using the recent experience at a single institution in which each tumor has been critically reviewed by a single pathologist. A secondary objective of this study was to determine whether the results of survival analyses in periampullary carcinomas were consistent with Whipple's hypotheses.

MATERIALS AND METHODS

A prospective database containing clinicopathologic data on all patients presenting to the surgical service at Memorial Sloan-Kettering Cancer Center with periampullary neoplasms was established in October 1983. This database was used to identify patients presenting with tumors of the ampulla of Vater between October 15, 1983 and June 30, 1995. Clinic notes, hospital charts, and pathology reports were reviewed. All histologic specimens from tumors of the duodenum, ampulla of Vater, distal bile duct, and periampullary pancreas were reviewed by a single pathologist. Ampullary tumors were defined as tumors grossly appearing to arise from the ampulla or microscopically demonstrating a preneoplastic component involving the ampulla. For smaller lesions, the tumor was confined within the ampulla (intraampullary) or to the mucosa and submucosa of the papilla. In larger tumors, there was often additional involvement of the periampullary duodenal mucosa and wall, the distal biliary and pancreatic ducts, or the underlying head of pancreas. Such cases were regarded as ampullary if the tumor was centered on the ampulla. Preneoplastic lesions (i.e., adenomas or areas of dysplasia) were helpful in supporting an ampullary origin when found by microscopy in the ampulla, but these were not invariably present. Tumors of duodenal, bile duct, or pancreatic origin were excluded from the ampullary analyses, and adenomas, neuroendocrine tumors, and islet cell tumors were excluded from the periampullary analyses.

A variety of clinicopathologic factors were examined with respect to patient survival in ampullary tumors. These included resection status, histologic subtype (intestinal morphology *versus* pancreaticobiliary morphology), American Joint Committee on Cancer T stage, tumor size, nodal metastases, surgical margins, transfusion, tumor grade, perineural invasion, and vascular invasion. Factors found to correlate with survival in ampullary tumors were compared in periampullary tumors. Univariate analyses were performed using the Kaplan-Meier method and log-rank test, and multivariate were performed by Cox proportional hazards regression. Comparison of proportions was performed using the Chi-square test and the Fisher exact test. Means were compared using the Student t test and analysis of variance.

RESULTS

Patients and Operations

One hundred twenty-three patients presented to Memorial Sloan-Kettering Cancer Center with carcinoma of the ampulla of Vater during this 140-month period, accounting for 6.8% of 1818 periampullary tumors. The mean age of those with ampullary cancer was 65.6 years (median, 66.9 yrs., range, 28.3–87.8 yrs.). The youngest patient was 28.3 years of age and was the only patient with familial adenomatous polyposis in this series. Sixty-seven (54.5%) were men and 56 were women (45.5%). The median follow-up of all patients with ampullary adenocarcinoma was 18.0 months (mean, 29.2 months, range, 0.3–138 months) and for resected patients was 22.4 months (mean, 33.5 months). Nine patients were lost to follow-up (four having more than 3 years, two patients with 1 to 3 years, and three patients with less than 1 year of follow-up). One hundred one patients had resection of ampullary carcinoma, 99 by pancreaticoduodenectomy and 2 by local excision (one of whom later underwent pancreaticoduodenectomy for recurrence). The resection rate was significantly higher in patients with ampullary carcinoma (82.1%) than in those with duodenal, bile duct, or pancreatic cancers presenting during the same period at our institution (Table 1). In the 22 patients whose tumors were not resected, 16 were explored and found to be unresectable or to have metastatic disease, whereas 6 were not explored based on the results of preoperative studies. Four patients whose tumors were resected had positive margins. The operative mortality rate (5%) and transfusion requirement (median, 250 ml, mean, 431 ml) in ampullary resections were not significantly different from those of other periampullary tumors. The median length of stay was 19.0 days (mean, 22.7, range, 8–91 days).

Table 1. RATE OF RESECTION OF PERIAMPULLARY TUMORS

Site	Total Pts	# Resected (%)	p *vs* Ampulla
Ampulla	123	101 (82.1)	-
Duodenum	85	39 (45.9)	<0.01
Bile duct	130	53 (40.8)	<0.01
Pancreas	1480	318 (21.5)	<0.01

Tumor Characteristics

The mean size of resected ampullary carcinomas was 2.7 cm (median 2.5 cm, range 0.3–10.3 cm). The rate of positive lymph nodes in patients with resected ampullary tumors was 45.5%, which was not significantly different than that seen for other resected periampullary cancers. Seventy-eight percent of resected ampullary cancers were well or moderately well differentiated, whereas 22% were poorly differentiated (not significantly different from other periampullary tumors). Sixty-three percent of ampullary tumors had an intestinal morphology, whereas 27% had a pancreatobiliary morphology (Figure 1). The intestinal type of ampullary carcinoma closely resembled primary adenocarcinomas of the colon and rectum. Simple and cribriformed glands were found with pseudostratified oval nuclei showing moderate degrees of atypia. Luminal necrotic debris was commonly present. The pancreatobiliary type more closely resembled primary adenocarcinomas of the pancreas and major bile ducts. Individual glands were more prominent, with a single layer of round, markedly atypical nuclei. Micropapillary areas were sometimes seen — as were individual infiltrating cells or small clusters of cells. A prominent desmoplastic stromal component was more commonly found in the pancreatobiliary type.

Survival Analysis

Resection was significantly correlated with survival, with a median survival of 58.8 months in resected patients (46% 5-year survival) *versus* 9.7 months in unresected patients (0% 5-year survival, $p < 0.01$; Figure 2). Factors that were significantly correlated with improved survival in resected tumors by univariate analysis included negative margins, well or moderate differentiation, and negative nodes (Table 2). When margins, differentiation, and nodal status were examined as covariates by Cox regression, only nodal status (Figure 3) and margins were independently correlated with survival. Clinicopathologic factors that did not influence survival in patients with ampullary carcinoma are listed in Table 3. Although there were large differences in median survival between groups of patients with respect to perineural invasion, histologic subtype, and vascular invasion, these differences did not reach statistical significance by univariate analysis.

When all patients with periampullary adenocarcinomas presenting to Memorial Sloan-Kettering Cancer Center during this time period were examined, overall survival was highest in those with ampullary carcinoma (Figure 4), as was their rate of resection (Table 1). When only resected periampullary tumors were analyzed, the median survival was highest in duodenal adenocarcinoma, followed by ampullary, bile duct, and pancreatic adenocarcinoma (Figure 5). The median survival rate was less than 10 months for all patients with periampullary adenocarcinoma that was not resected.

DISCUSSION

Adenocarcinoma of the ampulla of Vater is a relatively uncommon tumor that accounts for approximately 0.2% of gastrointestinal tract malignancies[23] or 7% of periampullary carcinomas in this study. Despite the relatively low incidence of these tumors, there have been numerous reports of ampullary adenocarcinoma in the literature (those series reporting more than 30 resections are summarized in Table 4). The largest study consisted of 459 patients collected from 57 centers in Japan between 1949 and 1974,[24] and the

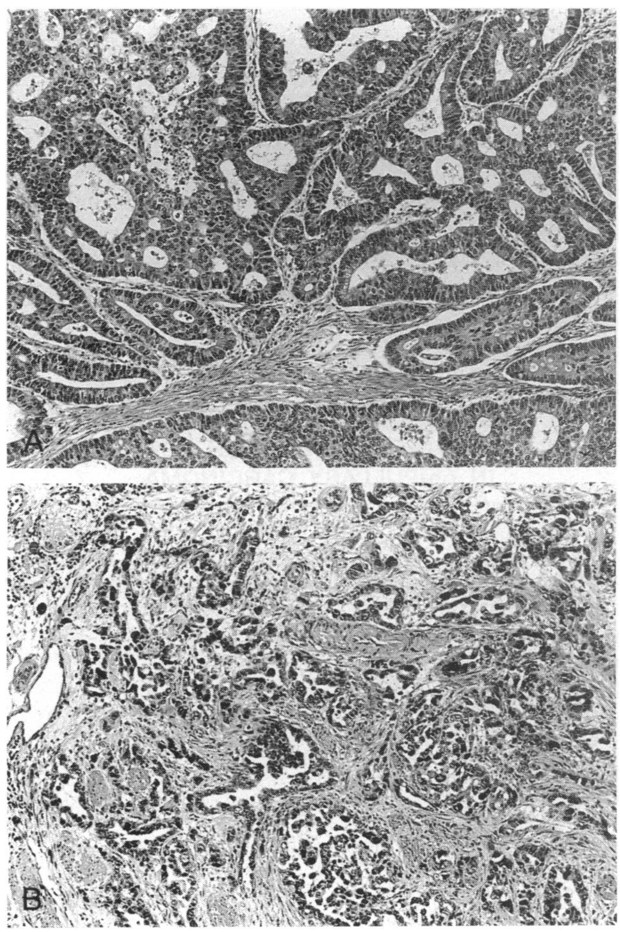

Figure 1. Ampullary adenocarcinoma with intestinal morphology (A) and pancreaticobiliary morphology (B).

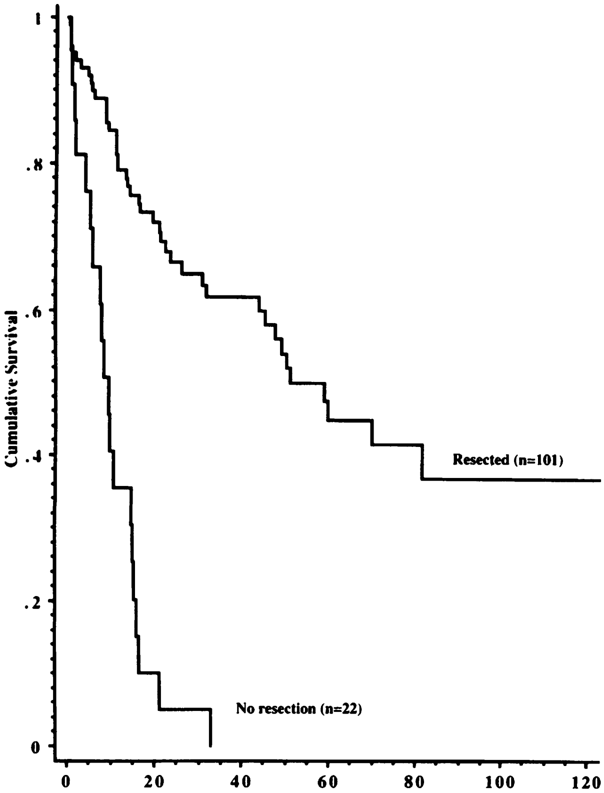

Figure 2. Survival of patients with resected ampullary carcinoma *versus* those not resected ($p < 0.01$, log-rank test).

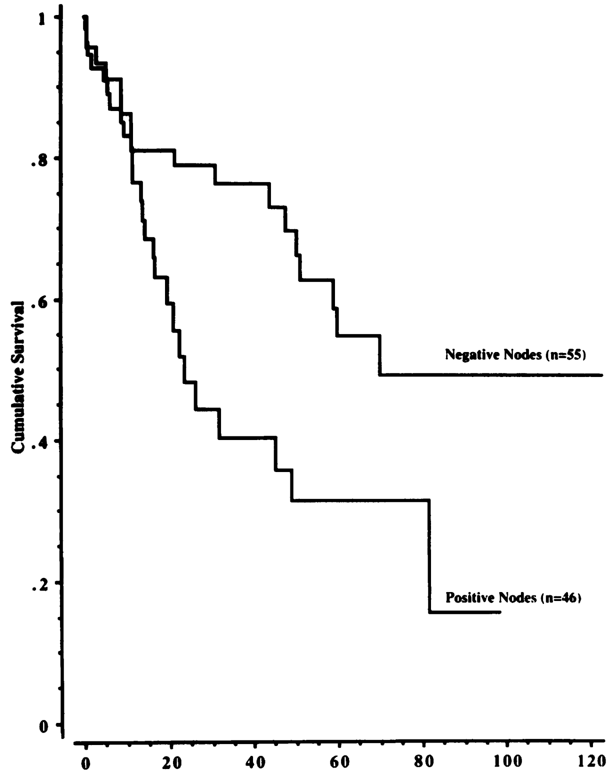

Figure 3. Survival in patients with resected ampullary carcinoma with negative and positive nodes ($p < 0.01$ by univariate analysis, $p = 0.04$ by multivariate analysis).

largest single institutional series have been reported from Johns Hopkins (120 patients from 1969–1996),[20] the Lahey Clinic (112 patients from 1942–1971),[10] and the Mayo Clinic (74 patients from 1965—1989).[19] This study represents another large series of ampullary adenocarcinoma from a single institution, with 123 patients cared for between 1983 and 1995.

Operative mortality in these series ranges from 1.5% to 25%,[22–25] and studies since 1990 have reported mortality rates below 8%. The overall rate of resection is 82.1% (913 of 1112 patients), which is identical to that found at Memorial Sloan-Kettering Cancer Center. The incidence of nodal metastases ranges from 29% to 52%,[10,22] with a mean of 40%.

Table 2. CLINICOPATHOLOGICAL FACTORS ASSOCIATED WITH SURVIVAL IN AMPULLARY CARCINOMA

Factor	# pts	Median Survival (months)	p value: Univariate Multivariate*
Resected	101	58.8	<0.01
Unresected	22	9.7	–
Margins negative	89	59.5	
Margins positive	4	11.3	<0.01 0.02
Negative nodes	55	69.7	
Positive nodes	46	23.6	<0.01 0.04
Well/Mod. diff	77	69.8	
Poor diff	22	20.8	<0.01 0.18

* Multivariate analysis performed for resected tumors only.

Table 3. CLINICOPATHOLOGIC FACTORS NOT CORRELATED WITH SURVIVAL IN AMPULLARY CARCINOMA

Factor	# pts	Medial Survival (months)	p value
No perineural invasion	82	58.8	
Perineural invasion	18	31.7	0.75
Size < 2 cm	51	50.9	
Size > 2 cm	50	58.8	0.69
No transfusion	47	not reached	
Transfusion	54	50.9	0.32
T1	22	not reached	
T2, T3	73	50.2	0.28
Intestinal subtype	56	59.6	
Pancreatobiliary subtype	23	22.5	0.23
No vascular invasion	66	69.8	
Vascular invasion	35	26.1	0.06

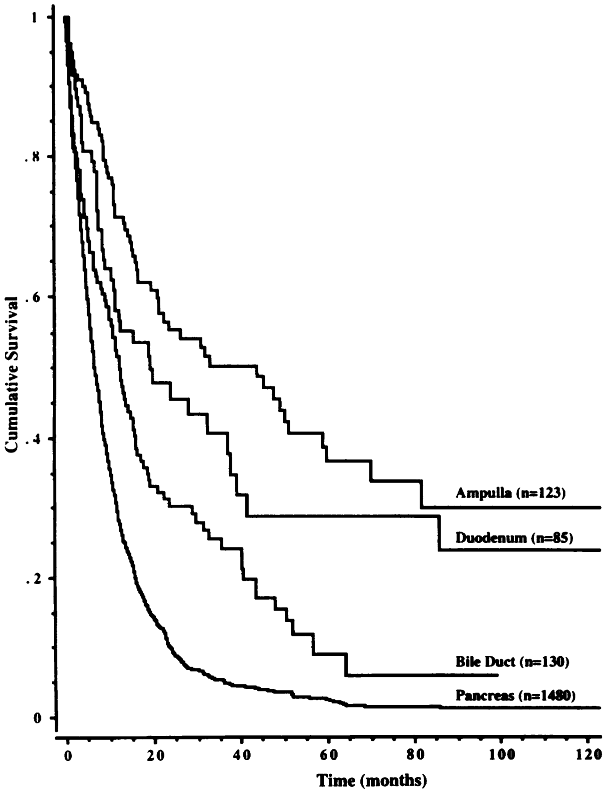

Figure 4. Overall survival calculated by the Kaplan-Meier method and log-rank test for periampullary carcinomas ($p < 0.01$).

There are wide variations in median survival and the percentage of 5-year survivors, with the lowest survival figures generally coming from series dating back many decades. Nakase et al.[24] reported a 5-year survival rate of only 6%, which may have been negatively influenced by their data being derived from 57 different institutions. The operative mortality in this study was 16%, and high operative mortality appears to be a factor in the diminished survival reported in other series.[26,27] Most of these studies include data from the 1940s to 1970s and therefore have not benefited from the improvements made in patient care over the past 2 decades. Most studies report 5-year survivals of 30% to 50% in resected patients, with the highest 5-year survival (58%) described by Trede et al.[17] and the highest median survival seen in the current series (58.8 months). Similar median survivals have been reported in smaller series of ampullary carcinoma by Martin et al.[28] (55.2 months, 23 patients) and Kellum et al.[29] (61.2 months, 17 patients).

In this study, resection, negative margins, negative nodes, and well-moderate differentiation predicted for improved survival by univariate analysis, and negative nodes and negative margins were independently correlated with survival in resected patients by multivariate analysis. Several studies confirm the significant association of nodal metastases,[12,19,20,23,28,30,31] tumor grade,[9,19,21,23] and margin status[22] with patient survival. Others have found that tumor stage,[9,23,31,32] tumor size,[30] perineural invasion,[18,33] lymphatic invasion,[19,33] venous invasion,[33] adjuvant chemotherapy,[18] and blood transfusion[20] were significantly correlated with survival. Most of these factors were included in the present analysis (except for adjuvant chemotherapy and lymphatic invasion) and were not significantly associated with survival.

One problem encountered with interpreting data from some studies is that they report survival rates after eliminating operative mortalities. In others, multivariate analysis has not been performed to identify independent risk factors correlating with patient survival. Although the recent report from Johns Hopkins found blood transfusion, lymph node status, and tumor differentiation to be significant by univariate analysis, none of these factors reached the threshold of significance by multivariate analysis.[20] Because these are not independent risk factors for patients with these tumors, it is difficult to make inferences for the prognosis of individual patients based on such results. Of the few other studies that performed multivariate analysis listed in Table 4, the only significant factor by multivariate analysis in Allema et al. was the margin of resection,[22] and by Monson et al.[19] (after exclusion of nonampullary cases) was lymphatic invasion. In a smaller series of 28 resected patients, Neoptolemus et al.[9] found both tumor grade and tumor stage (where stage IV was defined as lymph node involvement) to be significant by multivariate analysis.

Perhaps the most significant difficulty encountered in series reporting survival with periampullary neoplasms is

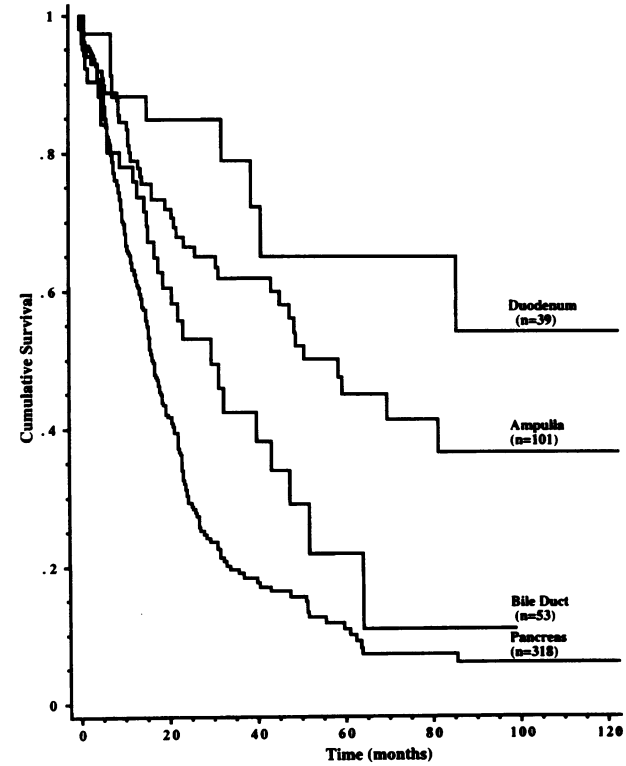

Figure 5. Survival in patients with resected periampullary carcinomas, as calculated by the Kaplan-Meier method and log-rank test ($p < 0.01$).

Table 4. COMPARISON OF SERIES OF AMPULLARY CARCINOMA

Author	Years	Operative Mortality (%)	# Pts./ Resected	% Positive Nodes	Median Survival* (months)	5 Year Survival (%)*
Warren (10)	1942–71	14.9	112/95	29	–	32
Nakase (24)	1949–74	16.0	459/351	–	22.7	6
Schlippert (26)	1940–76	21.1	57/38	33	24	10
Herter (42)	1940–78	14.7	45/44	–	25	28
Walsh (27)	1957–79	15.9	51/44	36.4	–	16
Jones (13)	1962–82	4.3	–/40	–		32
Knox (38)	1976–81	14.3	61/49	–	18	–
Tarazi (14)	1950–84	12.5	–/57		–	37
Hayes (25)	1949–85	25.0	35/31	45.2	–	53
Trede (17)	1972–89	2.4	–/36	–	–	58
Monson (19)	1965–89	5.7	–/74	31.3	33.6	34
Yamaguchi (33)	1969–89	7.9	40/38	47.2	–	–
Allema (22)	1984–92	1.5	–/67	52	–	50
Roder (23)	1983–94	4.5	69/66	42	41	35
Chareton (43)	1970–92	7.5	63/51	–	–	40
Talamini (20)	1969–96	3.8	120/106	39	46	38
Present Series	1983–95	5.0	123/101	45.5	58.8	46

* Resected patients.

that pathology slides are not routinely reviewed to confirm the site of origin of these tumors. This is often a difficult task and may be subject to some interpretation on the part of the pathologist. When Connolly et al. reviewed their 23 3-year survivors with presumed ductal adenocarcinoma of the pancreas at the University of Chicago they found that 29% of tumors could not be confirmed to have arisen in the pancreas, and that 17% did not have histologically proven cancer.[34] Nitecki et al.[35] reviewed the pathology of 31 3-year survivors with pancreatic ductal adenocarcinoma from the Mayo Clinic and found that 12 (39%) actually had other periampullary tumors and stressed the importance of pathologic re-review of pancreatic tumors when reporting survival data. Monson et al.[19] found that only 74 of 104 tumors initially thought to be ampullary carcinomas at the Mayo Clinic could be confirmed to have arisen from the ampulla. Seven were reclassified as having originated from the pancreas, 6 from the bile duct, 2 from the duodenum, and in 15, the origin could not be determined. Clearly, misclassification of tumors can and has impacted significantly on the outcome of survival analyses in series of periampullary tumors. The strength of the present study in contradistinction to a previous one from our own institution is that it includes 54 additional patients, has longer follow-up, and most importantly, includes tumors that were carefully reviewed by a dedicated gastrointestinal pathologist. As a consequence, in the present manuscript we found that resection, negative margins, and negative nodes were significantly correlated with improved survival, whereas only resection was significant in the previous study.[36]

There were only two patients with adenocarcinoma of the ampulla of Vater who underwent local resection in the present study, and one of these patients recurred within 22 months of the procedure despite pathologically negative margins. This individual had a pancreaticoduodenectomy performed with negative margins at a second procedure, but required a partial resection of the vena cava for local invasion. The number of patients undergoing local resection was too small to make comments on its advisability for adenocarcinoma, but other series have noted problems with recurrence. Branum et al.[37] reported recurrence in 6 of 8 patients with ampullary adenocarcinoma treated by local resection, Schlippert et al.[26] described 3 of 7 patients requiring reoperation for recurrence or duodenal obstruction, and Tarazi et al.[14] reported that 3 of 11 patients recurred after local resection. Knox and Kingston[38] suggested that 25 patients with ampullary carcinoma treated by local resection had a better 5-year survival than the 24 patients in their series treated by pancreaticoduodenectomy, but their operative mortality for pancreaticoduodenectomy was 30%. Four of their patients undergoing local resection subsequently died of metastatic disease, and two patients had local recurrence. Although this question has not been addressed by a prospective trial, it would appear that the role of local excision for adenocarcinoma of the ampulla of Vater is probably best limited to elderly and high-risk patients who may not tolerate pancreaticoduodenectomy.[21]

The finding that patients with ampullary carcinomas had the highest overall survival rate in periampullary neoplasms is undoubtedly related to their having the highest rate of resection. Because tumor size, grade, vascular invasion, and perineural invasion did not significantly impact on patient survival, and patients with nodal metastases had prolonged survival with resection (median, 23.6 months), an aggressive operative approach is warranted for all patients without evidence of distant metastatic disease. If one looks at survival after resection, patients with duodenal cancer survived longer than those with ampullary cancer. More than half of duodenal cancers were not resectable, however, diminishing the overall survival of this group. In resected duodenal tumors, patients with positive margins, positive nodes, or poorly differentiated tumors still had relatively long survival rates, confirming that aggressive surgical treatment should also be attempted in patients with duodenal cancers.[39] Conversely, in pancreatic cancer, survival was generally poor even when nodes and margins were negative or when tumors were well or moderately differentiated. Survival of patients with resected pancreatic ductal adenocarcinoma was similar to that reported previously from our institution (10.2% actual 5-year survival).[40]

One explanation for the observed patterns of survival in these periampullary tumors is that there are fundamental differences in tumor biology between these neoplasms. Whipple himself suggested that ampullary tumors were "better differentiated, of the adenomatous type, slower to invade the lymphatics and blood vessels."[4] In this study, there was a clear trend that duodenal cancers had the best survival and that pancreatic cancers the worst survival in almost all categories of resected tumors examined (which included margins, nodes, and differentiation). Survival of patients with ampullary tumors generally followed closely behind those with duodenal tumors, whereas survival of patients with bile duct tumors generally fell between those with ampullary and pancreatic cancers. Perhaps periampullary tumors represent a biologic spectrum of malignancies, where intestinal-type tumors (like duodenal cancer) comprise the biologically more favorable end of the spectrum and pancreaticobiliary tumors the other.

There are several lines of evidence that suggest that ampullary tumors are biologically more similar to intestinal than pancreatic cancers. First is the histologic appearance of ampullary tumors, which may have either an intestinal or pancreaticobiliary morphology. In this study, 70% of ampullary cancers had an intestinal morphology and showed a trend toward improved survival relative to the pancreatobiliary histologic subtypes (median survival of 59.6 *versus* 22.5 months, but this difference was not statistically significant). Second, the frequent finding of ampullary tumors in patients with familial adenomatous polyposis suggests that similar genetic alterations and mechanisms of carcinogenesis may be present in colonic and ampullary neoplasms from these patients. And third, K-ras mutations occur as a relatively early event in ampullary carcinoma, with a pattern and incidence (37%) similar to that seen in colon cancer.[41] This incidence is only approximately half of that seen in pancreatic carcinomas. Further genetic studies will be necessary to clarify the biologic basis for improved survival for patients with ampullary carcinoma.

Whipple's observation that patients with ampullary carcinoma have improved survival relative to those with pancreatic cancer because of earlier presentation is borne out by the significantly higher resectability rate seen in ampullary tumors in this study. One possible conclusion from this would be that ampullary tumors present at an earlier stage. Although the current American Joint Committee on Cancer staging systems for these tumors are not directly comparable, two potentially important factors that were examined in resected tumors were nodal metastases and tumor size. The rates of positive lymph nodes were not significantly different between resected periampullary tumors (ranging from 46% to 55%). The mean size of tumors was smallest in bile duct followed by ampullary carcinomas, and both pancreatic and duodenal cancers were significantly larger than ampullary tumors. Resected duodenal cancers were the largest and had the best survival, whereas resected bile duct tumors were on average the smallest and had the next to lowest survival. Therefore, differences in tumor size and the incidence of nodal metastases are not the only explanations for differences in survival seen in resected periampullary tumors. Although patients with small ampullary tumors may develop jaundice leading to early diagnosis, it would appear that there also are as yet undefined biologic factors that contribute to their improved survival.

References

1. Halsted WS. Contributions to the surgery of the bile duct passages, especially of the common bile duct. Boston Medical and Surgical Journal 1899;141: 645–654.
2. Cohen I, Colp R. Cancer of the periampullary region of the duodenum. Surgery, Gynecology and Obstetrics 1927;45: 332–346.
3. Whipple AO, Parsons WB, Mullins CR. Treatment of carcinoma of the ampulla of Vater. Ann Surg 1935;102: 763–779.
4. Whipple AO. A reminiscence: pancreaticoduodenectomy. Review of Surgery 1963;20: 221–225.
5. Brunschwig A. Resection of pancreas and duodenum for carcinoma-pancreatoduodenectomy. Surgery, Gynecology and Obstetrics 1937; 65: 681–684.
6. Whipple AO. Observations on radical surgery for lesions of the pancreas. Surgery, Gynecology and Obstetrics 1946;82: 623–631.
7. Trimble IR, Parsons JW, Sherman CP. A one stage operation for the cure of carcinoma of the ampulla of Vater and of the head of the pancreas. Surgery, Gynecology and Obstetrics 1941;73: 711–722.
8. Brennan MF. Surgical management of peripancreatic cancer. In: K. I. Bland, C. P. Karakousis and E. M. Copeland, eds. Atlas of Surgical Oncology. Philadelphia: W.B. Saunders Company; 1995:473–485.
9. Neoptolemus JP, Talbot IC, Carr-Locke DL, et al. Treatment and outcome in 52 consecutive cases of ampullary carcinoma. Br J Surg 1987;74: 957–961.
10. Warren KW, Choe DS, Plaza J, Relihan M. Results of radical resection for periampullary cancer. Ann Surg 1975;181: 534–540.
11. Cohen JR, Kuchta N, Geller N, et al. Pancreaticoduodenectomy: A 40 year experience. Ann Surg 1982;195: 608–617.
12. Lerut JP, Gianello PR, Otte JB, Kestens PJ. Pancreaticoduodenal resection: surgical experience and evaluation of risk factors in 103 patients. Ann Surg 1984;199: 432–437.
13. Jones BA, Langer B, Taylor BR, Girotti M. Periampullary tumors: which ones should be resected? American Journal of Surgery 1985; 149: 46–52.
14. Tarazi RY, Hermann RE, Vogt DP, et al. Results of surgical treatment of periampullary tumors: a thirty-five year experience. Surgery 1986; 100: 716–722.

15. Crist DW, Sitzmann JV, Cameron JL. Improved hospital morbidity, mortality, and survival after the Whipple procedure. Ann Surg 1987; 206: 358–365.
16. Michelassi F, Erroi F, Dawson PJ, et al. Experience with 647 consecutive tumors of the duodenum, ampulla, head of the pancreas, and distal common bile duct. Ann Surg 1989;210: 544–556.
17. Trede M, Schwall G, Saeger H-D. Survival after pancreaticoduodenectomy: 118 consecutive resections without an operative mortality. Ann Surg 1990;211: 447–458.
18. Chan C, Herrera MF, de la Garza L, et al. Clinical behavior and prognostic factors of periampullary adenocarcinoma. Ann Surg 1995; 222: 632–637.
19. Monson JRT, Donohue JH, McEntee GP, et al. Radical resection for carcinoma of the ampulla of Vater. Arch Surg 1991;126: 353–357.
20. Talamini MA, Moesinger RC, Pitt HA, et al. Adenocarcinoma of the ampulla of Vater: a 28-year experience. Ann Surg 1997;225: 590–600.
21. Robertson JFR, Imrie CW, Hole DJ, et al. Management of periampullary carcinoma. Br J Surg 1987;74: 816–819.
22. Allema JH, Reinders ME, van Gulik TM, et al. Results of pancreaticoduodenectomy for ampullary carcinoma and analysis of prognostic factors for survival. Surgery 1995;117: 247–253.
23. Roder JD, Schneider PM, Stein HJ, Siewert JR. Number of lymph node metastases is significantly correlated with survival in patients with radically resected carcinoma of the ampulla of Vater. Br J Surg 1995;82: 1693–1696.
24. Nakase A, Matsumoto Y, Uchida K, Honjo I. Surgical treatment of cancer of the pancreas and the periampullary region: cumulative results in 57 institutions in Japan. Ann Surg 1977;185: 52–57.
25. Hayes DH, Bolton JS, Willis GW, Bowen JC. Carcinoma of the ampulla of Vater. Ann Surg 1987;206: 572–577.
26. Schlippert W, Lucke D, Anuras S, Christensen J. Carcinoma of the papilla of Vater: a review of 57 cases. Am J Surg 1978;135: 763–770.
27. Walsh DB, Eckhauser FE, Cronenwett JL, et al. Adenocarcinoma of the ampulla of Vater: diagnosis and treatment. Ann Surg 1982;195: 152–157.
28. Martin M, Rossi RL, Dorucci V, et al. Cinical and pathologic correlations in patients with periampullary tumors. Arch Surg 1990;125: 723–726.
29. Kellum JM, Clark J, Miller HH. Pancreaticoduodenectomy for resectable malignant periampullary tumors. Surgery, Gynecology and Obstetrics 1983;157: 362–366.
30. Delcore R, Connor CS, Thomas JH, et al. Significance of tumor spread in adenocarcinoma of the ampulla of Vater. Am J Surg 1989;158: 593–597.
31. Mori K, Ikei S, Yamane T, et al. Pathological factors influencing survival of the ampulla of Vater. Eur J Surg Oncol 1990;16: 183–188.
32. Tsao JI, Rossi RL, Lowell JA. Pylorus-preserving pancreatoduodenectomy: is it an adequate cancer operation? Arch Surg 1994; 129: 405–412.
33. Yamaguchi K, Nagai E, Ueki T, et al. Carcinoma of the ampulla of Vater. Aust N Z J Surg 1993;63: 256–262.
34. Connolly MM, Dawson PJ, Michelassi F, et al. Survival in 1001 patients with carcinoma of the pancreas. Ann Surg 1987;206: 366–373.
35. Nitecki SS, Sarr MG, Colby TV, van Heerden JA. Long-term survival after resection for ductal adenocarcinoma of the pancreas: Is it really improving? Ann Surg 1995;221: 59–66.
36. Matory YL, Gaynor J, Brennan MF. Carcinoma of the ampulla of Vater. Surgery, Gynecology and Obstetrics 1993;177: 366–370.
37. Branum GD, Pappas TN, Meyers WC. The management of tumors of the ampulla of Vater by local resection. Ann Surg 1996;224: 621–627.
38. Knox RA, Kingston RD. Carcinoma of the ampulla of Vater. Br J Surg 1986;73: 72–73.
39. Rose DM, Hochwald SN, Klimstra DS, Brennan MF. Primary duodenal adenocarcinoma: a ten-year experience with 79 patients. J Am Coll Surg 1996;183: 89–96.
40. Conlon KC, Klimstra DS, Brennan MF. Long term survival following curative resection for pancreatic ductal adenocarcinoma: clinicopathological analysis of 5-year survivors. Ann Surg 1996;223: 273–279.
41. Howe JR, Klimstra DK, Cordon-Cardo C, et al. K-ras mutations in adenomas and carcinomas of the ampulla of Vater. Clinical Cancer Research 1997;3: 129–134.
42. Herter FP, Cooperman AM, Ahlborn TN, Antinori C. Surgical experience with pancreatic and periampullary cancer. Ann Surg 1982;195: 274–281.
43. Chareton B, Coiffic J, Landen S, et al. Diagnosis and therapy for ampullary tumors: 63 cases. World J Surg 1996;20: 707–712.