Carcinoma of the Ampulla of Vater

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Thirty-five consecutive cases of adenocarcinoma of the ampulla of Vater seen over the past 36 years were reviewed. The introduction of new diagnostic techniques over the course of this study improved the accuracy of preoperative diagnosis but did not lead to earlier diagnosis. The surgical resectability rate was 88%, and 53% of postoperative survivors were free of disease at 5 years. Of the 14 patients with metastases to regional lymph nodes, 27% survived disease-free for 5 years. Surgical mortality was 25% for the entire series but has been reduced to 6.6% over the past decade. Surgical mortality was primarily due to leakage of the pancreaticojejunostomy; the risk of pancreaticojejunostomy leak correlated inversely with the degree of chronic pancreatitis in the pancreatic remnant. In 35% of resected cases, a benign adenomatous component was contained within the cancer of the ampulla of Vater. Cure rates are good for this lesion. The most important factor in maximizing cure rate is careful attention to the technical details of pancreaticojejunostomy in order to minimize surgical mortality. Benign adenomas appear to be a frequent precursor of carcinoma of the ampulla of Vater.

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THE PERIAMPULLARY AREA is anatomically complex and adenocarcinoma may arise from one of four types of epithelium: the mucosa of the ampulla of Vater, the pancreatic duct, the distal common bile duct, or the periampullary duodenum. Carcinomas from each of these four sites of origin may exhibit different growth patterns and different natural histories. In the clinical situation, the site of origin cannot always be distinguished, and surgical treatment for all resectable carcinomas in the periampullary area is essentially the same. However, when reviewing the natural history, cure rates, and nuances of diagnosis and surgical care, it is advantageous to separate these four lesions as clearly as possible.

Carcinoma of the ampulla of Vater is considered together with other periampullary cancers in most reports.[1-4] Furthermore, the criteria by which a cancer is judged to be ampullary in origin has not always been clear in previous reports.[2-6] In our experience, histology is not always helpful in distinguishing among the various sites of origin; this distinction is best made on the basis of gross surgical anatomy. The natural history may be obscured by inclusion of large tumors that encompass the distal bile duct and ampulla and invade the periampullary pancreas and duodenal wall such that an ampullary origin cannot be assigned with confidence. Conversely, overly rigid criteria may cause all but the smallest and most favorable lesions to be excluded.

To clarify the presentation, natural history, surgical resectability, cure rate, and distinctive features of diagnostic work-up and surgical technique, we reviwed our experience with carcinoma of the ampulla of Vater.

Materials and Methods

Hospital files and pathology records were systematically searched and records were identified and reviewed of all patients classified as having neoplasms of the periampullary region, head of the pancreas, ampulla of Vater, distal bile duct, or duodenum. From this group, patients with neoplasms of the ampulla of Vater were selected, using the preoperative diagnostic evaluation, surgeon's note, gross pathologic description, histology, and often specimen photographs (Figs. 1 and 2). In most cases, the gross surgical pathology and specimen photographs were most helpful. Cases in which the mucosa of the ampulla of Vater could be clearly identified as the site of origin of the tumor (*i.e.*, tumor confined to the ampulla of Vater or clearly infiltrating out from it into

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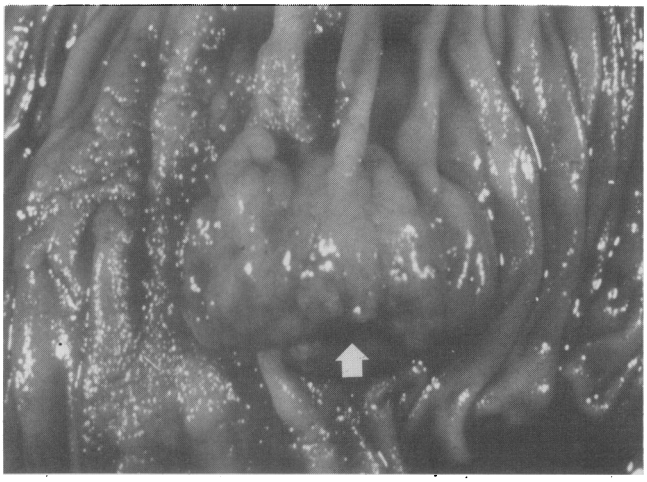


FIG. 1. Gross specimen of carcinoma of ampulla of Vater. The ampullary orifice is at the interior aspect of the tumor mass (arrow).

FIG. 2. Gross specimen of carcinoma of ampulla of Vater. The ampullary orifice can be seen in the center of the tumor mass (arrow).

the periampullary tissues) were included. Doubtful cases, where the site of origin could not be clearly assigned, were uncommon but were excluded from this series.

The cases were then submitted to intensive clinical and histopathologic review analyzing features of presentation, demographics, details of preoperative work-up, surgical treatment, postoperative follow-up, and histopathologic features. Survival rates were calculated by the product limit method of Kaplan and Meier.[7] Statistical comparisons were made using χ^2 analysis.

Results

Of 37 cases identified as neoplasms of the ampulla of Vater during the period of study (1949–1985), two were benign villous adenomas. The age of the 35 patients with malignant lesions ranged from 41 to 83 years with a median age of 62 years. Twenty-six patients were men and 11 women. The most common presenting signs are summarized in Table 1. The classic triad of fluctuating painless jaundice, palpable gallbladder, and anemia was present in only two patients. In nine patients, cholecystectomy had been performed within 10 months of diagnosis of carcinoma of the ampulla of Vater in the erroneous belief that the patients had only biliary stone disease.

Preoperative evaluation became much more accurate over the course of this study, largely due to the introduction of fiberoptic upper GI endoscopy and endoscopic retrograde cholangiopancreatography. An accurate preoperative diagnosis of carcinoma of the ampulla of Vater was established in 27% of patients prior to 1969, whereas after 1969 the preoperative diagnosis was correctly established in 73% of patients. However, the introduction of better diagnostic techniques did not improve the stage at diagnosis as judged by the status of the regional lymph nodes in resected specimens. Six of 17 patients prior to 1969 had positive nodes in their resected specimens, while eight of 14 patients after 1969 had positive nodes.

In 31 of 35 patients (88%) with malignant lesions, radical resections could be carried out (30 Whipple resections, 1 total pancreatectomy). In the remaining four patients, metastatic disease at presentation precluded radical resection and bypass alone was performed. One of two patients with benign villous adenomas underwent Whipple resection and the other underwent local resection. Of the 32 patients undergoing radical resection (31 for carcinoma, 1 for villous adenoma), there were eight postoperative deaths (25%). Postoperative mortality declined steadily throughout the period of study (Table 2) and over the past decade has been 6.6 ($p < 0.05$, comparing the last 10 years of study with the previous years of study). The causes of the surgical mortality are listed in Table 3. By far the most common cause of perioperative mortality was intra-abdominal sepsis due to leakage of the pancreaticojejunostomy. Of nine confirmed pancreaticojejunostomy leaks, six proved fatal.

TABLE 1. *Presenting Symptoms and Signs of Ampullary Carcinoma*

	(%)
Jaundice	81
Weight loss	70
Abdominal pain	62
Occult blood in stool	45
Anemia	38
Anorexia	35
Pancreatitis	5

TABLE 2. *Surgical Mortality by Decade: Radical Pancreaticoduodenectomy for Carcinoma of the Ampulla of Vater*

Decade	Cases	Deaths	Mortality Rate (%)
1949–1955	1	0	0
1956–1965	5	1	20
1966–1975	11	6	54
1976–1985	15	1	6.6
Total	32	8	25

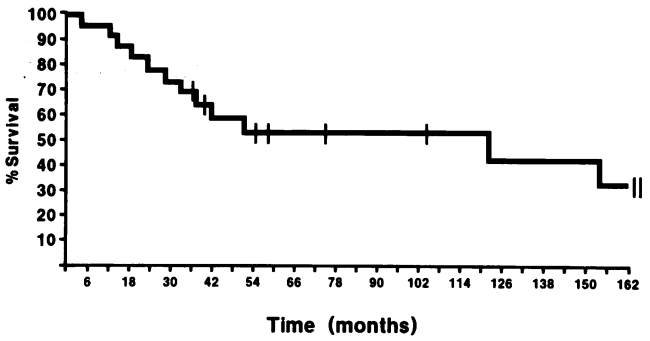


FIG. 3. Disease-free survival, patients with carcinoma of the ampulla of Vater surviving radical resection for cure. Tic marks signify the length of follow-up of patients who remain under active follow-up.

To further investigate the perioperative mortality, all factors that might influence leakage of the pancreaticojejunostomy were examined in detail. We studied leak rates by surgeon, configuration of reconstruction, anastomotic technique, quality of the pancreatic remnant, and use of ductal stents or surgical drains. Pancreaticojejunostomy leakage strongly correlated with the quality of the pancreatic remnant. In 10 patients with evidence of obstructive pancreatitis (dilated pancreatic duct, fibrosis of the pancreas as noted by the surgeon or pathologist, and/or preoperative increased serum amylase) there were no pancreaticojejunostomy leaks, while in the remaining 21 patients with a soft, normal pancreas undergoing Whipple resection (1 patient having a total pancreatectomy is excluded) the leak rate was 43%. This difference was statistically significant ($\chi^2 = 4.3$, $p < 0.05$). No other factor correlated statistically with the development of pancreaticojejunostomy breakdown. Over the past decade, only one of 15 patients developed a pancreaticojejunostomy leak, and this patient survived.

Excluding postoperative deaths, the five-year disease-free survival rate was 53% and the 10-year survival rate was 42% (Fig. 3). Median follow-up of patients who remain under active follow-up is 58 months. Fourteen patients (45%) had metastatic carcinoma involving lymph nodes in the resected specimen. These patients had a 5-year disease-free survival rate of 27% and a median survival of 37 months.

Only 12% of patients undergoing radical resection had a vagotomy added to the procedure. In almost all cases, a conservative gastrectomy (consisting only of the antrum of the stomach) was performed, such that 78% of the patients undergoing radical resection had neither a vagotomy nor an extensive (greater than 50%) gastrectomy. Although two patients developed stress upper GI hemorrhage associated with pancreaticojejunostomy leak and intra-abdominal sepsis, no patient developed symptomatic ulcers beyond the immediate postoperative period.

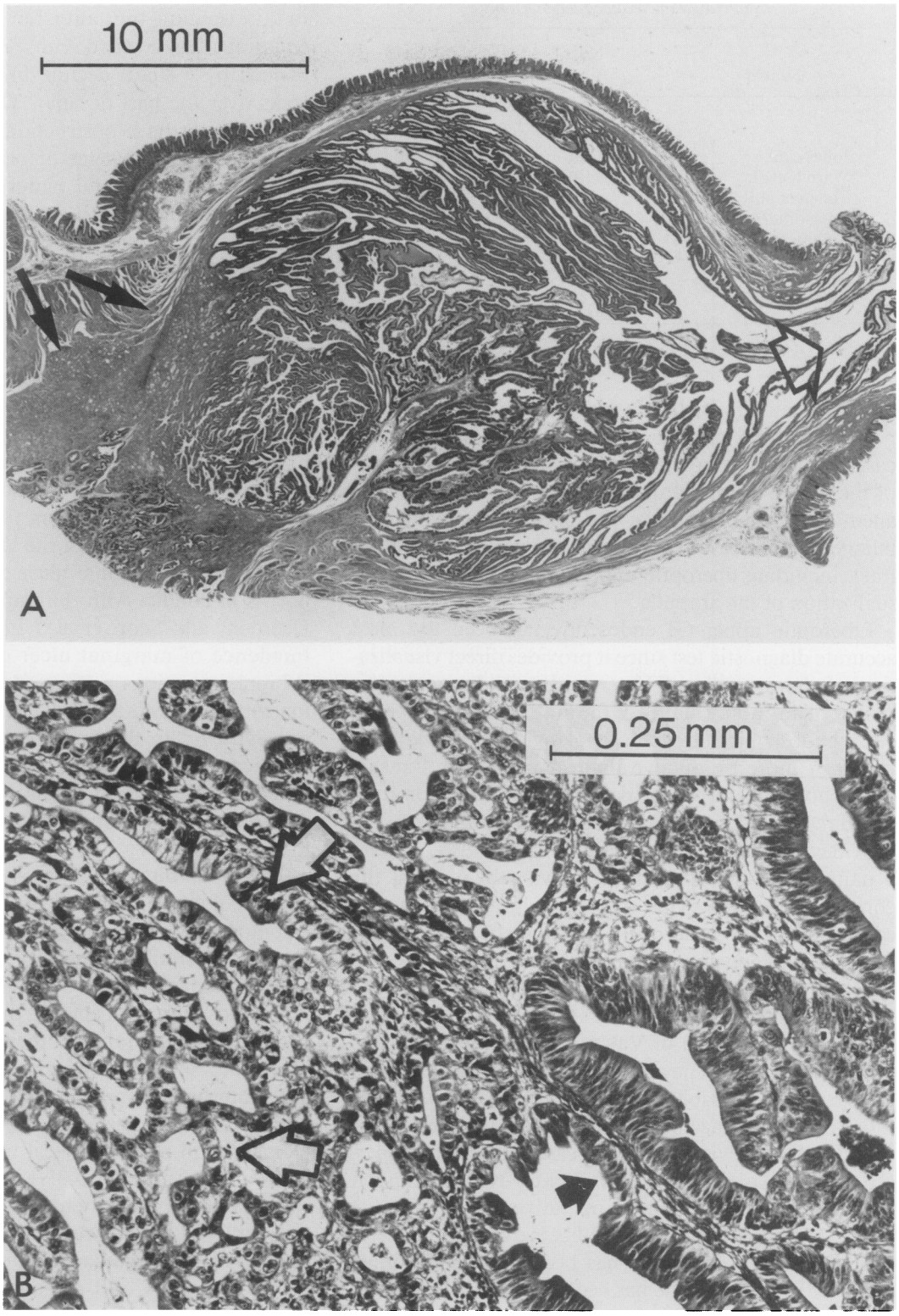
Histologically, carcinomas were classified as primarily infiltrating in 27 patients (84%) and as papillary in five patients (16%). In 11 of 31 specimens (35%) in which adequate tissue was available for detailed analysis, a benign adenomatous component was associated with the invasive carcinoma (Fig. 4A). These adenomatous components consisted of well-defined benign tubular or villous epithelial components in a broad vascularized stroma. Features of pseudostratification, increased nuclear/cytoplasmic ratio, loss of basal orientation, intraglandular budding and bridging, and increased mitoses were present in all cases to a variable degree (Fig. 4B). The presence of a benign adenomatous component correlated with size of the malignant portion of the tumor, being present in 48% (11 of 23) of patients with carcinomas less than 3 cm in size and 12% (1 of 8) in those greater than 3 cm in size.

TABLE 3. *Causes of Operative Mortality: Radical Pancreaticoduodenectomy for Carcinoma of the Ampulla of Vater*

Complications	No. of Deaths
Pancreaticojejunostomy leak	6
Liver abscess	1
Cerebral vascular accident	1
Total	8

Discussion

Diagnostic accuracy improved significantly over the course of the study with the introduction of fiberoptic upper GI endoscopy, ultrasonography, endoscopic retrograde pancreatography, and percutaneous transhepatic cholangiography. In our experience, ultrasonography has been the most helpful initial screening examination for the patient who presents with obstructive jaundice. The finding of stones within the gallbladder or common bile duct indicates the likelihood of primary biliary stone disease and suggests the need for cholecys-



FIGS. 4A and B. Microphotograph of adenoma of ampulla in association with invasive cancer. *A*. Villous tumor, with foci of carcinoma (closed arrows) (original magnification ×5). The ampullary orifice is to the right (open arrows). *B*. High power view of 4A, showing villous tumor (closed arrow) and carcinoma (open arrows) (original magnification ×250).

tectomy and common bile duct exploration without further evaluation. Stones and carcinoma of the ampulla may coexist, however, (they coincide in 12 of 37 patients in this series) underlining the importance of careful evaluation of the ampulla at the time of common duct exploration for presumed stone disease. Helpful intraoper-

TABLE 4. *Five-year Survival of Patients with Ampullary Carcinoma Surviving Pancreaticoduodenectomy*

Source	No. of Cases	5-Year Survival
		(%)
Jones et al.[3]	36	36
Warren et al.[6]	109	32
Cohen et al.[11]	22	38
Coutsoftides et al.[12]	8	50
Kellum et al.[13]	12	50
Crane et al.[14]	21	42
Grace et al.[15]	18	62
Current series	31	53

ative maneuvers include the Kocher maneuver with palpation of the ampulla, choledochoscopy, and on occasion, duodenotomy for direct visualization and biopsy of the ampulla. In addition, the preoperative finding of anemia or occult blood in the stool in a patient with biliary stone disease requires further work-up of the GI tract, including fiberoptic upper GI endoscopy with visualization of the ampulla.

Fiberoptic upper GI endoscopy has been the most accurate diagnostic test since it provides direct visualization of the ampulla of Vater and provides access for biopsy of any abnormality of the ampulla. In our experience, endoscopic retrograde cholangiopancreatography has been more productive than percutaneous transhepatic cholangiography for patients with distal common bile duct obstruction as defined by ultrasound, since it provides a direct look at the ampulla, and also provides a pancreatogram in addition to visualization of the common bile duct. This may be helpful in excluding carcinoma of the head of the pancreas by virtue of the absence of pancreatic ductal stricture.

In view of the long delay in nine patients in our series who had cholecystectomy prior to discovery of the carcinoma of the ampulla of Vater, we had hoped that the introduction of the newer diagnostic modalities would lead to a demonstrably earlier diagnosis as reflected in a more favorable stage of tumors in the latter part of our series. This however was not the case. Accurate preoperative diagnosis is still desirable, however, because it helps the surgeon to plan the operative procedure.

The 25% postoperative mortality is cause for concern. Fortunately, this mortality has been steadily declining and over the past decade has been 6.6%. Our experience of a declining mortality for pancreaticoduodenectomy parallels that of other institutions where a relatively large experience with lesions in the periampullary area can be accumulated by a relatively small number of surgeons. Better anesthesia, antibiotics, intensive care, and perioperative nutritional care have all played a role in this declining mortality, but improvement in surgical technique has been the most important factor (as evidenced by a sharp decline in pancreaticojejunostomy leaks over the past decade). The majority of these patients do not have obstruction of the duct of Wirsung with secondary changes of pancreatic ductal obstruction, pancreatitis, and pancreatic fibrosis.[8] In these cases, anastomosis of the soft pancreas, the capsule of which does not hold sutures well, is less secure. To our knowledge, this is the first report to show in a statistically significant way that the status of the pancreatic remnant strongly influences the fate of the pancreaticojejunostomy. Our efforts to provide a more secure pancreaticojejunostomy have centered around good mobilization of the transected end of the pancreatic remnant, invagination of the cut end of the pancreas into jejunum in preference to a duct to mucosa anastomosis, and use of horizontal mattress nonabsorbable sutures to lessen the chance of suture tearing through the soft pancreas resulting in dehiscence of the anastomosis.

The lack of marginal ulcer complications in this report is in conflict with the findings of Grant and VanHeerden[9] and Scott et al.[10] In those reports a 6–36% incidence of marginal ulcer complications followed Whipple resections performed without an accompanying truncal vagotomy; furthermore, the marginal ulcers were virulent in their course and were responsible for significant morbidity and mortality. We have not experienced this complication and continue to employ conservative gastric resections without vagotomy in the majority of cases.

The 5-year disease-free survival rate is gratifying. Carcinoma of the ampulla of Vater is the most curable of all carcinomas of the upper gastrointestinal tract. Others have noted similar survival rates when reviewing carcinoma of the ampulla of Vater separate from other periampullary lesions (Table 4). In view of this relatively high surgical cure rate and the lack of effective adjuvant treatment, surgeons must be careful to maximize the cure rate by minimizing the perioperative mortality. Even in the presence of metastatic involvement of regional lymph nodes, surgical resection can be curative. Therefore, limited involvement of adjacent nodes should not preclude attempts at resection. We have not yet employed pylorus preservation in patients with carcinoma of the ampulla of Vater undergoing pancreaticoduodenectomy, out of concern that preservation of the pylorus might compromise the resection of regional nodes. However, we are following with interest recent reports suggesting that cure rates for carcinoma of the ampulla of Vater are not lessened by preserving the pylorus.[16]

The association of benign adenomas with invasive carcinoma of the ampulla has been noted by Baczako et al.[17] and Kozuka et al.[18] The known association of periampullary adenoma and carcinoma with familial polyposis syndromes and the finding in this and the previously mentioned series of a frequent association of adenoma and carcinoma of the ampulla of Vater in patients without familial polyposis suggests that an adenoma-to-carcinoma sequence may also play a role in the development of the more common nonfamilial form of carcinoma of the ampulla of Vater. Ryan et al.,[19] in a recent review, found that most duodenal villous lesions occurred at or near the ampulla of Vater. They speculated that carcinogens in the bile or pancreatic secretions might explain the finding of such a large portion of villous lesions of the ampulla in comparison to other areas of the duodenum and proximal small bowel.

Furthermore, the finding in this series that large cancers of the ampulla do not as frequently have an associated adenomatous component raises the possibility that an advancing invasive carcinoma might overgrow a precursor benign adenoma in some instances. If this assumption is correct, our finding of a benign adenoma in conjunction with invasive carcinoma in 35% of the cases would be a minimum estimate of this association. The low incidence of carcinoma of the ampulla of Vater does not make screening feasible, but the frequent association of adenoma and carcinoma in our series leads us to view with concern the occasional finding of a benign villous adenoma in the ampullary area. Because a negative endoscopic biopsy does not exclude the possibility of carcinoma within the adenoma, we believe that these should be excised in every instance. In some cases, this can be accomplished with a local resection, but Whipple resection should be carried out if the adenoma is not amenable to local resection and the patient is a good operative risk.

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