Hypothsis: This study was designed to evaluate prospectively oncological factors determining survival after resection of tumors of the papilla, comparing local and radical oncological resection. We hypothesized that, in malignant lesions of the ampulla, the T and N stages are major determinants of the patient's long-term outcome.

Background Data: The frequency of malignant lesions in adenomas of the papilla is about 26%. Villous adenoma of the ampulla is considered a premalignant lesion. Local excision has been recommended for benign adenoma and pancreatoduodenectomy for malignant lesions.

Patients and Methods: From January 1, 1982, through June 30, 1997, 171 patients with tumors of the ampulla of Vater were surgically treated. Demographics, intraoperative factors, tumor pathological findings, and postoperative short- and long-term follow-up data were documented prospectively. Of the patients, 45 had adenoma of the papilla and 126 had malignant lesions of the ampulla.

Results: Local resection was performed in 40 of the 45 patients with adenoma. In 98 of the 126 patients with malignant lesions, a radical Kausch-Whipple resection or pylorus-preserving pancreatoduodenectomy was used. Of the patients with benign adenoma, 40 had local resection and 5 had pylorus-preserving pancreatic head resection, with a hospital mortality of 0%. Thirty of 35 patients had villous adenoma, 9 (30%) of the 30 with severe dysplasia. Of the 126 patients with malignant lesions, 98 had partial pancreatoduodenectomy and 10 had ampullectomy, with an overall hospital mortality of 3.1% for patients who underwent resection. Seventy-eight of the 98 patients had an R0 resection. The 5-year survival probability for all patients who underwent resection was 84% for cancer stage I, 70% for stage II, and 27% for stage III. In 8 patients with villous adenoma and carcinoma in situ and in 10 patients with cancer in the adenoma, ampullectomy with local lymph node dissection was performed. In 4 of the patients who had villous adenoma and a carcinoma in stage pT1 NO, an R0 resection was performed, resulting in cure of cancer. On the basis of a multivariate regression analysis, the prognosis after oncological resection of cancer of the ampulla is determined by the absence of lymph node metastasis (P < .05), the absence of infiltration into the pancreatic head tissue (P < .05), and the application of an R0 resection.

Conclusions: In patients with villous adenoma of the ampulla, ampullectomy was an adequate surgical treatment. In patients with a low-risk cancer in stages pTis and pT1 NO M0, G1 or G2, a local resection with ampullectomy including local lymph node dissection is justified. An oncological resection of cancer of the ampulla by means of a pylorus-preserving partial pancreatoduodenectomy or the Kausch-Whipple resection is the surgical procedure of choice; the 3- and 5-year survival rates were 72% and 52%, respectively, in patients with R0 resections.

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PATIENTS AND METHODS

Between January 1, 1982, and June 30, 1997, 171 patients with tumors of the ampulla of Vater were surgically treated. In the 15-year period, 45 patients with benign tumors of the papilla and 126 with cancer of the papilla were operated on. In the adenoma group, 20 (44%) of the patients were male and 25 (56%) were female; in the carcinoma group, 71 (56.3%) were male and 55 (43.7%) were female. The mean age of the adenoma patients was 59 years, ranging from 18 to 81 years; in the cancer group the mean age was 63 years, with a range of 33 to 89 years.

SURGICAL TECHNIQUES

Resection of the papilla was performed in 3 patients with benign lesions. Resection of the papilla included removal of the intraduodenal roof and the intraluminal common orifice of the papilla without the need for reinsertion of the common bile and pancreatic main duct entrance into the duodenal wall.

An ampullectomy was performed in 37 patients with neoplastic lesions. The technique of ampullectomy is described elsewhere and is based on the following principal surgical steps: (1) resection of biliopancreatic junction and of some pancreatic head tissue and (2) reinsertion of the common bile duct and the pancreatic main duct into the duodenal wall. In patients with severe dysplasia or a pT1 low-risk cancers, an additional lymph node dissection was performed, including the anterior and posterior lymph nodes of the pancreatic head and the supraduodenal lymph nodes along the foramen of Winslow.

Eighty-eight patients underwent major oncological resection by means of the Kausch-Whipple technique or a pylorus-preserving partial pancreateoduodenectomy (PPPD). The lymph node dissection in each patient included removal of the following lymph node regions: anterior and posterior head, supraduodenal, common and proper hepatic artery, hepatoduodenal ligament, and lymph nodes to the right of the superior mesenteric artery.

DEFINITION OF SURGICAL PRINCIPLES

Partial pancreateoduodenectomy was defined as resection of pancreatic head, duodenectomy, and resection of flexura duodenoejunalis; lymph node dissection, including anterior and posterior head, supraduodenal area, common and proper hepatic artery, hepatoduodenal ligament, and lymph nodes right of the superior mesenteric artery; resection of the lower common bile duct up to the common hepatic duct; and reconstruction with the first jejunal loop, pancreateojunal anastomosis end to side, and hepatojejunal anastomosis end to side. In patients with pylorus-preserving resection (PPPD), end-to-side anastomosis was performed, duodenum to jejunum. Kausch-Whipple resection (pPD) consisted of Billroth-II resection of the stomach and Braun enteron Anastomosis. R0 resection indicates resection margins of the pancreas, common bile duct, duodenum, and retropancreatic tissue histologically free of carcinoma; R1 resection, histologically positive for carcinoma cells in a resection margin. Radical resection was partial pancreateoduodenectomy plus lymph node dissection plus retroportal, retropancreatic fatty tissue dissection.

FOLLOW-UP AND HISTOLOGICAL REEXAMINATION

The primary criterion of the prospective follow-up in the study was survival time; follow-up examinations took place at 3, 6, and 12 months; 2, 3, 4, and 5 years; and yearly after 5 years. Patient follow-up was completed August 31, 1997.

Histological examination of the operative specimens and biopsy material was performed twice and by 2 different pathological investigators. The first examination was done by a staff pathologist in charge of gastrointestinal tract histopathology. The second pathological investigator (T.M.) performed a blinded reexamination.

STATISTICAL ANALYSIS

Patient demographics, intraoperative factors, tumor pathology, and postoperative follow-up data were evaluated in both univariate and multivariate models to determine their impact on long-term survival. Survival analysis was done by the method of Kaplan-Meier. Differences in survival between subsets were compared by the log-rank test. Multivariate analysis was performed with the Cox proportional hazards model. Differences among subgroups of the cohort were evaluated with a 1-way analysis of variance. Results are reported as mean ± SD and median percentiles. Significance was accepted at the 5% level.

Thirty-seven percent of the patients with a malignant tumor and 22% of those with a benign lesion of the ampulla were aged 70 years or older at the time of operation; 40% of the patients who had an ampullectomy for ampullary cancer and 68% of those who had only a biliary and/or gastric bypass procedure were aged 70 years or older when operated on. The median time of the patients’ symptoms caused by the lesion of the papilla was 8 weeks in the adenoma group and 5 weeks in the patient group with carcinoma. The clinical manifestations in the patients with adenoma (n = 45) and carcinoma (n = 126) were as follows, respectively: epigastric pain, 25 (56%) and 59 (47%); jaundice, 13 (29%) and 93 (74%);
loss of body weight, 5 (11%) and 67 (53%); and nausea and vomiting, 19 (42%) and 79 (63%). Diabetes mellitus was observed in 8 (18%) of 45 patients with adenoma and in 23 (18%) of 126 patients with carcinoma.

The diagnostic accuracy in patients with an adenoma of the papilla was highest with the use of duodenoscopy and multiple biopsies, in terms of the diagnosis of tumor of the papilla. However, when the final histological diagnosis after surgical treatment was compared with the preoperative histological findings on biopsy, diagnostic accuracy was only 74%. In patients with cancer of the ampulla, the sensitivity of duodenoscopy and multiple biopsies was 40%, and the diagnostic accuracy was 78% (Table 1). The histological probes of the preoperative biopsy specimens and of the surgical specimens were reevaluated by a second, independent pathologist specializing in the gastrointestinal tract (T.M.).

Forty-five patients had benign tumors. In terms of the final histological findings, 35 patients had adenomas; 30 (86%) of these 35 patients demonstrated villous adenomas; 10 patients suffered from other types of lesions, eg, tumorlike adenomyosis and neurinoma. In patients with adenoma, final histological examination disclosed a tubular adenoma in 5, a villous adenoma in 14, and a tubulovillous adenoma in 16 cases. The dysplasia was graded mild in 20% (7 of 35 patients), moderate in 51% (18 of 35 patients), and severe in 29% (10 of 35 patients). Except for 5 patients, a local resection procedure was used in patients with benign tumors of the papilla. In 37 patients, ampullectomy was performed, with the need for reinsertion of the common bile duct and pancreatic main duct into the duodenal wall. Patients with a villous adenoma and a macroscopically based suspicion of malignant neoplasm (tumor >2 cm in maximum diameter, video documentation [since 1985] of ulcerations in adenoma) had an additional local lymph node dissection including the anterior and posterior lymph nodes of the pancreatic head and the supraduodenal lymph nodes. Five patients with suspected carcinoma underwent pylorus-preserving pancreatic head resection with lymph node dissection. No patient died of the surgical treatment. After surgery, the median follow-up of the patients with benign tumors was 43 months. Forty patients had no abdominal complaints or a local recurrence of the adenoma; 1 patient died at the age of 92 years of cardiac insufficiency. Median hospitalization time was 22 days for the whole group.

CANCER OF THE PAPILLA

One hundred twenty-six patients had malignant lesions of the papilla. Final histological diagnosis was carcinoma in 125 patients and carcinoid of the papilla in 1. When the patients were classified according to the pTNM staging (Union Internationale Contre le Cancer [UICC], 1993), 18% had stage I, 31% had stage II, 44% had stage III, and 7% had stage IV. The degree of cell differentiation was high in 3.1% (G1), moderate in 74.7% (G2), and low in 22.2% (G3). Fifty-seven patients (45.6%) showed no lymph node metastasis. Sixty-nine patients were pN positive; in these patients, a median of 18 lymph nodes (range, 5-35) were assessed. The resection rate was 77.8%. Seventy-eight patients had an R0 resection. Hospital mortality was 3.2% (3 of 93 patients) in patients with pancreatoduodenectomy and 0% in patients after ampullectomy for cancer. After radical resection, an intra-abdominal complication occurred in 25% of the patients; 6 of 88 patients had another operation, and in 2 patients a total pancreatectomy was completed during the second operation (Table 2).

pTNM STAGE AND PROGNOSIS

Among the patients with ampullary cancer in whom a local or radical resection was performed, none had a distant metastasis at operation. Considering the patients with an oncological radical resection (PPPD or Kausch-Whipple resection), the survival rate after 5 years was 84% for patients with stage I disease, decreasing to 70% for stage II and 27% for stage III; no patients with stage IV disease survived for more than 1 year after operation (Figure 1). The differences in survival rate between stage I and stage II (P<.04) and stage III and stage IV (P<.006) were highly significant.

EFFECT OF CANCER INVASION INTO THE PANCREATECTOMY ON PROGNOSIS

Cases of pT1 and pT2 cancer are considered on the basis of UICC definitions as cases without infiltration into pancreatic tissue, in comparison with pT3 and pT4, where tumor infiltration into the head of the pancreas has oc-
curred. In the 50 patients without pancreatic invasion (pT1 and pT2), the survival rate was 87% at 3 years and 79% at 5 years. Among the 76 patients with cancer invasion into the pancreatic head, however, the 3- and 5-year survival was 40% and 24%, respectively (Figure 2). The differences in survival rates between these 2 groups were significant ($P < .002$).

LYMPH NODE METASTASIS AND PROGNOSIS

Fifty-seven (45%) of 126 patients had no lymph node metastasis and 69 patients had cancer cells in the lymph nodes on the basis of hematoxylin-eosin staining and histological examinations. The prognosis of the patients without lymph node metastasis was significantly better (3-year and 5-year survival, 72% and 63%, respectively) than that of the patients with lymph node metastasis (26% and 21%, respectively) (Table 3 and Figure 3).

CORRELATION BETWEEN HISTOLOGICAL CELL DIFFERENTIATION AND PROGNOSIS

Patients who had a high or moderate degree of cell differentiation (G1 and G2) showed a significantly better 3- and 5-year survival than patients with a G3 degree of differentiation (Figure 4).

PROGNOSIS AFTER LOCAL RESECTION

In 10 patients a local resection was performed by means of ampullectomy completed by a local lymph node dissection. Four patients were operated on for villous adenoma, but on final histological examination they had carcinoma in the adenoma. In 6 patients a small adenocarcinoma was treated by ampullectomy; however, on the final histological examination this was an R1 resection. Because of the high degree of comorbidity and the high risk and advanced age of the patients (5 of the 6 were older than 70 years), an additional radical surgical procedure was not performed. After ampullectomy, no patient died; 3 of 4 patients after R0 ampullectomy were still alive at 7, 6, and 1.5 years; 1 patient died 6 years after resection following decompensation of liver cirrhosis without recurrence, but no patient with an R1 resection survived for 3 years (Table 4 and Figure 5).

PROGNOSIS AFTER RADICAL RESECTION

Before 1990, a partial pancreatoduodenectomy by means of the Kausch-Whipple technique was the standard procedure for all patients with carcinoma of the ampulla of Vater. Since 1990, a PPPD was performed in most patients. The survival rate at 3 years was 72% in the patients with PPPD and 52% in those with Kausch-
Whipple resection, because the latter was applied more frequently in patients with advanced cancer stage.

**COMMENT**

There are substantial arguments for the hypothesis of an adenoma-dysplasia-carcinoma sequence of neoplastic lesions of the ampulla of Vater. The frequency of a malignant lesion in a villous adenoma of the ampulla is observed to be 25% and higher. In most of the carcinomas of the ampulla, tissue samples from adenomas were found in the stage of severe dysplasia. Of patients with a villous adenoma in this series, 16.6% finally displayed a cancer in the adenoma.

Recent advances in diagnostic techniques, such as duodenoscopy with multiple biopsies, and the use of endoscopic ultrasonography provide a precise preoperative diagnosis with regard to the nature and extent of the tumor. However, a single endoscopic biopsy has been reported to miss the diagnosis in 40% to 60% of cases. Therefore, after the diagnosis of ampullary tumor is established, the most important diagnostic step is to assess the presence or absence of a carcinoma and the presence and extent of severe dysplasia. Most of the patients will have multiple endoscopic measures and multiple biopsies. Endoscopic ultrasonography has a particular advantage for the detection of invasion of the tumor into the duodenal wall and the pancreas and the occurrence of regional lymph node enlargement or metastases. Accuracy rates of 78% to 87% have been reported for the diagnosis of pancreatic invasion and of 54% to 83% for the diagnosis of regional lymph node metastasis, with the additional use of endoscopic ultrasonography.

In patients with a carcinoma in situ or a T1 cancer in the villous adenoma, 6% to 10% have lymph node involvement. Moreover, frozen section performed at the time of operation often fails to identify a cancer in the villous adenoma or cancer infiltration of the lymph node. Therefore, it seems to be nearly impossible to assess with certainty in each patient the presence of a carcinoma in situ or an infiltrating carcinoma in the adenomas without complete excision. Only in cases of a small tubular adenoma is an endoscopic snare excision justified; in all patients with a villous adenoma or a tubulovillous adenoma, surgical excision is mandatory because of the association with a carcinoma in situ or a pT1 cancer.

**LOCAL EXCISION OF pT1 CANCER OF THE AMPULLA**

In 1899, Halsted performed the first local extirpation of a carcinoma of the papilla. In patients with a pT1 cancer, local resection or ampullectomy has been advocated as being equal to or better than pancreatoduodenectomy. The ampulla of Vater has a distinct pattern of lymphatic drainage and, in contrast to pancreatic tumors with a diffuse lymphatic spread, tumors of the papilla and ampulla tend to involve a local group of lymph nodes near the ampulla, even in advanced cases. These morphological features make ampullary lesions a distinct clinical entity, yielding a substantially superior prognosis if the infiltration does not include the pancreatic tissue. In case of an adenoma with a carcinoma in situ or a pT1 N0 M0 cancer of the ampulla, a local resection is indicated, except in patients who have a high-risk G3 or G4 cancer. Therefore, the low-risk group is defined as those with a carcinoma in situ and a pT1 N0 M0, G1 or G2 cancer. If intraoperative findings show a cancer more advanced than T1 and a node-positive or higher G3 or G4 grade tumor, the procedure would have to be extended to a partial pancreatoduodenectomy, and this should even be true if postoperatively an adenoma or a T1 N0 cancer had to be reclassified by full histological evidence as pT2 N-positive, or if a poorly differentiated T1, G3 carcinoma was found. In this series of adenomatous lesions of the ampulla, treated surgically, an ampullectomy was performed in 8 patients with severe dysplasia consid-

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**Table 4. Local Resection of Villous Adenoma With Severe Dysplasia or Cancer Within Adenoma in 18 Patients**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Histological Findings</th>
<th>No. of Patients</th>
<th>Resection, No. (%)</th>
<th>Hospital Mortality, %</th>
<th>Alive Without Cancer, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampullectomy Adenoma + severe dysplasia/cancer in situ*</td>
<td>8</td>
<td>8 (100)</td>
<td>0 (0)</td>
<td>0</td>
<td>71</td>
</tr>
<tr>
<td>Partial pancreatoduodenectomy Adenoma + pT1 cancer</td>
<td>10</td>
<td>4 (40)</td>
<td>6 (60)</td>
<td>0</td>
<td>R0: 3; R1: 0‡</td>
</tr>
<tr>
<td></td>
<td>Adenoma + pT1 cancer</td>
<td>5</td>
<td>5 (100)</td>
<td>0 (0)</td>
<td>5</td>
</tr>
</tbody>
</table>

*Severe dysplasia in a villous adenoma is classified as cancer in situ neoplasia.
†One patient died of cancer and treatment-unrelated disease.
‡Median survival, 18 months.
In 1912, Kausch reported the first successful 2-stage pancreatic head resection, to our knowledge, in a patient with carcinoma of the ampulla. Today, the PPPD is the surgical procedure of choice in patients with cancer of the ampulla. The partial pancreatoduodenectomy includes resection of the duodenum, the distal common bile duct, and the head of the pancreas in combination with the lymph node dissection around the head of the pancreas, including N1 and N2 lymph nodes according to the Japanese classification of lymph node regions in cancer of the ampulla. Hospital mortality after PPPD is less than 5% in recently published series. Patients with a UICC stage I or stage II cancer have a significantly better prognosis after partial pancreatoduodenectomy than patients with cancer stage III or IV. With respect to the results of PPPD in the present series, the survival rate at 3 years was 72% for patients who received a pylorus-preserving resection and 52% for those who received a partial pancreatoduodenectomy. While these findings are not strictly comparable because of differences between periods, the results demonstrate that, at least to date, PPPD has not had unfavorable effects on prognosis. Nakase et al investigated the incidence of lymph node metastasis in 54 patients who had undergone partial pancreatoduodenectomy for carcinoma of the ampulla of Vater, finding the incidence of infrapyloric lymph node metastasis to be 3.7%. Accordingly, if no metastasis is confirmed in the infrapyloric lymph node by intraoperative frozen section examination, PPPD can be used for carcinoma of the ampulla of Vater.

ONCOLOGICAL FACTORS IN PROGNOSIS

The differences in survival rates after surgery between the 2 groups, classified on the basis of lymph node metastasis or extension of the cancer to the pancreatic head tissue, clearly reflect prognosis, and the 2 factors were significantly correlated (Table 5). Regional lymph node metastasis was seen in only 22% of the patients who had pT1 and pT2 cancer, whereas the proportion rose to 60% in patients with pT3 and pT4 cancer. These findings suggest that pancreatic invasion indirectly indicates the status of regional lymph node metastasis. The prognostic significance of pancreatic invasion in carcinoma of the ampulla of Vater has been reported by other investigators. Kawarada et al and others reported the incidence of lymph node metastasis around the superior mesenteric artery to be 15.6% in carcinoma of the ampulla of Vater, and they showed the lymphatic pathways from posterior pancreatoduodenal lymph nodes to para-aortic lymph nodes via lymph nodes around the superior mesenteric artery. In 1984, Hanyu reported that extended lymph node dissection improved prognosis, showing a higher 5-year survival rate (81%) in patients who had undergone complete lymph node dissection around the superior mesenteric artery, compared with 40% in patients who had received incomplete tissue dissection around it. Therefore, an extended lymph node clearance should be considered as an additional procedure for patients with pancreatic invasion including the lymph nodes on both sides of the superior mesenteric artery. However, more controlled data are needed about the oncological impact of extended lymph node dissection.

The chance of cure after the use of partial pancreatoduodenectomy including removal of the local lymph nodes is around 50%. In recently published series, the 1-year survival is around 80%, the 3-year survival around 55% to 60%, and the 5-year survival around 35% to 50%. The application of an R0 resection is the surgeon's contribution to increase 5-year survival. The median survival after R0 resection was around 45 months in this series. To improve the prognosis for patients with pancreatic invasion, further resection including extended lymph node removal is a recommended additional procedure.

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REFERENCES


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ARCHIVES OF INTERNAL MEDICINE

Sympathetic Activation in Heart Failure and Its Treatment With β-Blockade
Gregory S. Pepper, MD; Richard W. Lee, MD

Multiple models explaining the pathogenesis of heart failure have been put forth during the past 5 decades. These models were modified as clinical evidence supported or refuted their assumptions. During the past 2 decades, heart failure models emphasized the importance of neurohormonal systems in heart failure progression. The positive impact that angiotensin-converting enzyme inhibitors have had on mortality from heart failure has bolstered the neurohormonal theory. Attention recently has turned to the sympathetic nervous system and its potential deleterious effects on the cardiovascular system in heart failure. The sympathetic nervous system can negatively impact the cardiovascular system in heart failure in several ways, including down-regulating β1-receptors, exerting direct toxic effects on the myocardium, and contributing to myocardial remodeling and life-threatening arrhythmias. β-Adrenergic blockers have shown promise for reducing morbidity and mortality in heart failure, but definitive reductions in mortality remain to be shown by future investigations. (1999;159:225-234)

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