

# Carcinoma of the Ampulla of Vater:

## Review of 38 Cases with Emphasis on Treatment and Prognostic Factors

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Thirty-eight cases of carcinoma of the ampulla of Vater are presented. The diagnosis has been confirmed at laparotomy in all patients. Three operations were done, a pancreaticoduodenal resection in 23 patients, a biliary-enteric bypass in 7 patients and a biliary-enteric bypass plus excision of tumor in 8 patients. The operative mortality was 8% following resection, 14% following bypass plus excision of the ampulla and 13% following biliary-enteric bypass. Five patients survived 5 or more years. The longest survivors have followed pancreaticoduodenal resections (131 and 216 months). The level of bilirubin or presence of pain did not correlate with prognosis. Prognosis was better in the absence of nodal metastases, and in the presence of papillary tumors.

CARCINOMA of the ampulla of Vater is an uncommon gastrointestinal malignancy that is found in 0.2% of all postmortem examinations.<sup>1</sup> Although often included in a classification of pancreatic carcinoma, ampullary tumors have been thought to be more favorable lesions. Whether this is due to biological factors, earlier onset of symptoms, earlier diagnosis, or because metastases occur later than with pancreatic carcinoma is presently unknown.

At the Cleveland Clinic between June 1955 and December 1974, the diagnosis of carcinoma of the ampulla of Vater was made in 38 patients. All patients underwent an abdominal operation. The definitive diagnosis was made at surgery in all patients and reconfirmed at autopsy in 19 patients. Some of these patients have been included in a previous report on ampullary and bile duct tumors.<sup>2</sup>

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### Clinical Information Materials

Of the 38 patients, 17 were men and 21 were women. The youngest patient was 28 years of age and the oldest was 79 years. The mean age of these patients at the time of diagnosis was 59.5 years. The mean age for women was 62 years and men 57 years.

### Symptoms

The common presenting symptoms included jaundice, weight loss, and pruritus. Jaundice, the most common symptom, was present in 32 patients. Six patients did not have jaundice by clinical or laboratory examination. The jaundice was persistent in 27 patients and intermittent in only 5 patients. Weight loss, the second most common symptom, was present in 21 patients. The mean weight loss per patient was 18 pounds. Pruritus, abdominal pain, anorexia, nausea, vomiting, fever and chills followed in descending order of frequency (Table 1).

### Signs

Jaundice was present and detectable in 32 patients. Hepatomegaly was present in 19 patients with the liver edge palpable 1 to 8 cm. below the right costal margin. Courvoisier's sign, a palpable gallbladder was present in only 5 patients (Table 2).

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Submitted for publication October 14, 1975.

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TABLE 1. *Presenting Symptoms*

Presenting Symptoms	Number of Patients
Jaundice	32/38
Weight loss	21/38
Pruritus	19/38
Abdominal pain	9/38
Nausea	6/38
Anorexia	8/38
Vomiting	4/38
Fever, Chills	4/38

### Laboratory Data

Abnormal tests are summarized in Table 3. Stool was tested for occult blood in only 10 patients, but was positive in all 10. The serum amylase level was elevated in 6 patients (Table 3).

### Roentgenograms

Roentgenograms of the upper gastrointestinal tract were obtained in 24 patients. The findings were normal in 13 and abnormal in 11. The abnormalities were non-specific and included deformity and dilatation of the second portion of the duodenum, gastric retention, compression of the first part of the duodenum, a filling defect at the region of the ampulla, an abnormal duodenal C loop, and abnormal mucosa in the second part of the duodenum.

### Treatment

All 38 patients underwent an abdominal operation. The procedure and results are summarized in Table 4. These included a biliary enteric bypass in 7 patients (cholecystoenteric or choledochenteric), a biliary intestinal bypass plus local excision of the ampullary tumor in 8 patients and a pancreaticoduodenal resection in 23 patients.

### Early Mortality

Four of the 38 patients died in postoperative period; 2 died after a pancreaticoduodenal resection; the third died after a biliary bypass and the fourth after a biliary bypass and excision of the tumor.

### Pancreaticoduodenal Resection

Of the 23 patients who underwent a pancreaticoduodenal resection (all with a pancreaticojejunal

TABLE 2. *Presenting Signs*

Presenting Signs	Number of Patients
Jaundice	32/38
Hepatomegaly	19/38
Palpable gallbladder	5/38

anastomosis) 12 had no local or regional lymph node metastasis at the time of surgery. The mean survival for this group was 55 months (excluding the 2 postoperative deaths). Of the 7 patients with regional lymph node metastasis, the mean survival was 23 months. Of these 23 patients, 14 are dead (autopsy revealed widespread metastasis in 12), 7 are alive at 12, 18, 24, 36, 44, 131 and 216 months, with a mean survival of 68 months. Only 4 have survived for more than 5 years. Two of our patients were lost to followup shortly after surgery, and have not been included in the follow-up and 2 died postoperatively because of gastrointestinal hemorrhage and infection.

### Bypass and Local Excision

Eight patients underwent a biliary enteric bypass plus excision of the ampullary tumor. Four had no gross evidence of local or distant metastasis and 2 had biopsy proven lymph node metastasis. The mean survival of the patients without metastasis was 42 months (excluding the 1 postoperative death) and with metastasis was 13.5 months. Of the 8 patients, 7 are dead. One died one month postoperatively of sepsis and gastrointestinal hemorrhage, 5 of metastasis and 1 of myocardial infarction. One is alive at 34 months after operation.

### Bypass Alone

Seven patients underwent biliary enteric bypass and 5 are dead of metastasis. In 4, no gross evidence of metastasis was present at surgery and these patients lived 24, 42, 30 and 72 months (mean 42 months). One patient with gross evidence of metastasis at the time of surgery died 6 months later. One other patient in this group died of gangrene of the leg 2 months after the biliary enteric bypass and 1 month after vascular surgery for this occlusion. Autopsy was performed in 5 patients and revealed widespread metastasis in all. Only 1 patient has survived for more than 5 years.

### Discussion

Although carcinoma of the ampulla of Vater is a well recognized tumor, difficulty is still encountered in its diagnosis, and surgical treatment is controversial. There were no unusual presenting features in these cases. At least 40% of patients<sup>3</sup> (42% in this series) have painless jaundice, persistent or fluctuating. Pain was present in 9 of 38 patients. Although some authors<sup>4</sup> have stated that the outlook is more favorable for patients with fluctuating jaundice, this was not corroborated in this series. The presence of pain has been felt to indicate tumor invasion and consequently a poorer survival.<sup>5</sup> This correlation between pain and survival was not present in this series. There was also no correlation between pain,

TABLE 3. Laboratory Test Results

Serum Bilirubin in mg/100 ml	Alkaline Phosp. Bodansky Units	Serum Amylase Somogi Units	HB Gram/100 ml	Stool for Occult Blood
Elevated in 32 patients Normal in 6	Elevated in 30 pts. Normal in 8	Elevated in 8 pts. Normal in 30	Hb > than 12 in 30 pts Hb < than 12 in 8 pts	Tested in 10 positive in 10 pts

resectability rates, and metastases. The surprising symptom in 21 of 38 patients was significant weight loss. Although characteristic of pancreatic carcinoma, particularly lesions arising in the uncinate process, the mean weight loss in these patients was 18 pounds. This, too, did not correlate with resectability or prognosis. An unexplained observation was the failure to establish preoperatively an accurate diagnosis. Despite the widespread use of duodenoscopy at this institution, we did not establish a positive diagnosis by this method in any of these patients. Since 1974, however, 2 patients have had a positive diagnosis of ampullary carcinoma made by duodenoscopy and biopsy.

The laboratory studies were of limited help in that they indicated cholestatic jaundice. Roentgenographic studies did not specifically localize the ampullary lesion except in one instance, and their nonspecific findings have been reported by others.<sup>4</sup> The definitive diagnosis of ampullary cancer has been made in this series by open surgical biopsy. There are two theoretical objections to this procedure. First, it involves a duodenotomy incision with the possible complications of sepsis and fistula formation if a pancreaticoduodenal resection is not possible, and second, the theoretical objection to spilling tumor cells with resulting intraperitoneal implantation does exist. Open intraoperative biopsy may also prolong the operative time, although this objection is of less importance. To overcome these objections preoperative or intraoperative endoscopic biopsies may help in planning of operation and establish a diagnosis.<sup>6</sup>

Although establishing a diagnosis may be difficult, deciding what operation to do has created considerable controversy. Three operations have been employed to treat ampullary cancer: biliary enteric bypass (a cholecystojejunostomy or cholecystoduodenostomy) biliary enteric bypass and excision of the ampullary tumor, and pancreaticoduodenal resection, or more recently total pancreatectomy. There are no published controlled studies that compare these operations. In this series patients older than 65, with coexisting serious medical conditions (i.e., cardiac or pulmonary disease or patients with detectable metastasis at surgery), usually underwent a biliary enteric bypass procedure with or without ampullectomy. It is therefore not completely valid to compare the results of these operations with the more radical procedure. At the very least, the bias of selection would favor patients undergoing the radical operation since their general health,

more favorable lesions and absence of invasion or metastases by themselves are better prognostic signs.

Regardless of the type of operation, three observations can be made: 1) the cause of death in nearly all patients has been metastases; 2) regardless of the type of operation, when regional lymph nodes are involved by tumor, mean survival is  $\frac{1}{2}$  to  $\frac{1}{3}$  of that when lymph nodes are not involved; 3) there were few differences in mean survival regardless of the operation. Although the only long-term survivors were those who had pancreaticoduodenal resection, the mean survival for all patients after pancreaticoduodenal resection was 55 months when lymph nodes were not involved by tumor. Two patients who have survived 11 and 18 years had papillary lesions without nodal metastasis. Even after a pancreaticoduodenal resection, survival was halved (23 months) when lymph nodes were involved. When a biliary enteric bypass with ampullectomy was done, the mean survival was 13 months less than for patients who underwent a pancreaticoduodenal resection. This applied to patients whose lymph nodes were not involved. The small number of patients with lack of randomization do not lend themselves to accurate statistical analyses. This was particularly so in patients with positive lymph nodes in the bypass group with or without ampullectomy since the number of patients were so few. Douglas<sup>6</sup> reviewed 5 reports that included 502 patients with ampullary cancer: the resectability rate was 64%. The mortality rate was 19% following pancreaticoduodenal resection and the 5-year survival was 26%. The mean survival for resected patients was 36 months.

More recently Warren, et al.<sup>7</sup> summarized their vast experience with the radical pancreaticoduodenal resection. One hundred and twelve patients with ampullary cancer were examined between 1942 and 1971. In 10% of cases ampullary tumors were intraoperatively misdiagnosed as pancreatic cancer. The operative mortality

TABLE 4. Results of Surgery

	Pancreaticoduodenal	Biliary Bypass	Bypass plus, Ampullectomy
No. patients	23	7	8
Operative mortality	2 (8%)	1 (14%)	1 (12%)
No metastasis at surgery	12	4	4
Mean survival	55 mon	42 mon	42 mon
With metastasis	7	1	2
Mean survival	23 mon	6 mon	13.5 mon

for the radical resection was 15%. The 5-year survival was 32%. Twenty per cent of patients had regional lymph node metastasis. The 5 and 10-year survival in patients without lymph node involvement was 40% and 35%. When lymph nodes were involved, the 5-year survival was only 9%. Wise, et al.<sup>3</sup> recently reported on 62 patients with periampullary cancer.<sup>3</sup> The mean 5-year survival following pancreaticoduodenectomy with positive lymph nodes was 12% and with negative nodes 29%. In patients who underwent local excision, it was 38% and following a palliative bypass the mean survival was 12 months. These data suggested a positive correlation between prognosis and age (patients less than 60 had a longer survival than those past 60). The age factor did not alter the survival statistics in our study. Our colleagues, Crile, Isbister and Hawk<sup>2</sup> reported 28 cases of ampullary cancer. There was a correlation between histology and 5-year survival. For papillary tumors 26% of the patients survived 5 years, whereas only 4% with infiltrating tumors survived this long. The mean survival for patients with papillary tumors was 31 months as compared to 23 months for those with infiltrating lesions. In this series, the mean survival was 39.5 months for patients with papillary tumors and 20 months for those with infiltrating tumors, and the only long term survivors in our series (11 and 18 years) had papillary tumors without lymph node involvement. Although all available reports provide useful data on ampullary cancer they do not answer the questions on how to treat an individual patient who has ampullary cancer. The recurring theme in most studies indicates that noninfiltrating or non-metastatic ampullary tumors are associated with a prognosis that is twice as good as with infiltrating or metastatic tumors. In selected older patients with localized tumors, ampullectomy with or without bypass provides results equal to or better than a pancreaticoduodenal resection.<sup>3</sup>

Although 5-year survivors are reported after radical

resections when nodal or regional metastases are present, the number of 5-year survivors is less than the operative mortality in most series.<sup>7</sup> In our series only 5 patients in the entire group survived 5 or more years. All had noninfiltrating papillary lesions without nodal metastases. Four have had a pancreaticoduodenal resection and one a bypass procedure. Two have died of metastases and one was lost to follow-up, and two are living. Thus, it is important to screen and select candidates for the pancreaticoduodenal resection because 5-year survival in the presence of regional or lymph node metastases is limited.

Immunotherapy and chemotherapy as adjuvant measures have not been emphasized by most authors, and we have had little experience with these modalities. Three patients were treated with 5 fluorouracil but little prolongation in life or objective remissions were seen in these patients.

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