Adjuvant Chemoradiotherapy for “Unfavorable” Carcinoma of the Ampulla of Vater

Preliminary Report

Vivek K. Mehta, MD; George A. Fisher, MD, PhD; James M. Ford, MD; Joseph C. Poen, MD; Mark A. Vierra, MD; Harry A. Oberhelman, MD; Augusto J. Bastidas, MD

Hypotheses: Adjuvant chemoradiotherapy decreases the risk of local recurrence in patients with adenocarcinoma of the ampulla of Vater and high-risk features. Adjuvant chemoradiotherapy for this population can be administered safely and without much morbidity.

Design: Controlled, prospective, single-arm study.

Setting: Tertiary care referral hospital.

Patients: From June 1995 to March 1999, 12 patients (7 men and 5 women; median age, 66 years; age range, 38-78 years) with “unfavorable” ampullary carcinoma were treated with adjuvant chemoradiotherapy. All patients underwent pancreaticoduodenectomy, and all pathologic findings were confirmed at Stanford University Medical Center, Stanford, Calif. Unfavorable features were defined as involved lymph nodes (n=10), involved surgical margins (n=1), poorly differentiated histological features (n=3), tumor size greater than 2 cm (n=6), or the presence of neurovascular invasion (n=4).

Interventions: Four to 6 weeks after undergoing pylorus-preserving pancreaticoduodenectomy with regional lymphadenectomy, patients began adjuvant chemoradiotherapy consisting of concurrent radiotherapy (45 Gy) and fluorouracil by protracted venous infusion (225-250 mg/m² per day, 7 days per week) for 5 weeks.

Main Outcome Measures: Local recurrence, distant recurrence, overall survival rate, and treatment-related toxic effects.

Results: All patients completed the prescribed treatment course. Toxic effects were assessed twice a week during treatment and graded according to the National Cancer Institute Common Toxicity Criteria Scale. One patient required a treatment interruption of 1 week for grade III nausea/vomiting. No grade IV or V toxic effects were observed. At median follow-up of 24 months (range, 13-50 months), 8 of 12 patients were alive and disease free. One patient was alive but had disease recurrence. Three patients died of this disease (liver metastases). Actuarial overall survival at 2 years was 89%, and median survival was 34 months. One surviving patient developed a local recurrence and a lung lesion. Actuarial overall survival and median survival were better than in a parallel cohort with resected high-risk pancreatic cancer (n=26) treated with the same adjuvant chemoradiotherapy regimen (median survival, 34 vs 14 months; P<.004).

Conclusions: Adjuvant chemoradiotherapy for carcinoma of the ampulla of Vater is well tolerated and might improve control of this disease in patients with unfavorable features.


From the Department of Radiation Oncology (Drs Mehta and Poen), the Division of Medical Oncology, Department of Medicine (Drs Fisher and Ford), and the Division of Surgical Oncology, Department of Surgery (Drs Vierra, Oberhelman, and Bastidas), Stanford University Medical Center, Stanford, Calif.

CARCINOMA of the ampulla of Vater is a relatively uncommon malignancy. Seventy percent of patients with carcinoma of the ampulla of Vater and poor prognostic features will fail and ultimately die of the disease. Kopelson and associates1 reviewed pooled data on 80 patients with ampullary cancers after potentially curative resection and found that 54% developed local-regional recurrence. Theoretically, adjuvant therapy may have the greatest benefit in patients with tumors at high risk of local recurrence. There has been interest in developing protocols for adjuvant therapy, but these efforts have been limited by the rarity of this disease. In 1994, we established an adjuvant treatment approach for patients with ampullary carcinoma with “unfavorable” features. We report on toxic effects and the preliminary results of our treatment regimen of adjuvant chemoradiation for ampulla of Vater carcinoma.

See Invited Critique at end of article

Seventeen patients underwent pancreaticoduodenectomy at Stanford University
PATIENTS AND METHODS

Between July 1995 and March 1999, all patients referred to Stanford University Medical Center, Stanford, Calif, with presumed pancreatic and peripancreatic malignancies were evaluated by a multidisciplinary gastrointestinal tumor board after a pretreatment staging evaluation that included a complete blood cell count, serum chemistries, serum tumor markers, chest radiography, and computed tomography of the abdomen. Seventeen patients underwent pylorus-preserving pancreaticoduodenectomy with a regional lymphadenectomy. Lymphadenectomy included all tissue to the right side of the superior mesenteric artery and extended just above the superior aspect of the left renal vein. Aortocaval nodes and tissue extending from the right ureter to the left side of the aorta and down to the origin of the inferior mesenteric artery were resected.

All pathological specimens were carefully reviewed, and carcinoma of the ampulla of Vater was confirmed. Patients were stratified into “favorable” and “unfavorable” disease presentations. Patients were considered to have unfavorable features if there was evidence of involved lymph nodes, involved surgical margins, poorly differentiated histological features, tumor size greater than 2 cm, or the presence of neurovascular invasion. Tumors without any of these features were considered favorable. Five patients with favorable tumor characteristics were observed after surgery. Twelve patients (7 men and 5 women) with unfavorable features were offered and accepted treatment with an adjuvant chemoradiotherapy regimen. The group that received postoperative chemoradiotherapy consisted of patients with at least one unfavorable feature, including involved lymph nodes (n=10), involved surgical margins (n=1), poorly differentiated histological features (n=3), tumor size greater than 2 cm (n=6), or the presence of neurovascular invasion (n=4).

Adjuvant treatment was initiated as soon as adequate oral nutrition could be restored, typically 4 to 6 weeks after the definitive surgical procedure. All patients received an explanation of anticipated acute and late toxic effects in verbal and written form. Informed consent was obtained. Nutritional counseling was provided before initiating treatment. Use of oral nutritional supplements to maintain an appropriate energy (caloric) intake was encouraged.

All patients were treated isocentrically with a medical linear accelerator using 6- or 15-MV photons and 3 to 4 custom-shaped fields. Treatment volumes generally included the pancreas, porta hepatis, celiac, pancreaticoduodenal, and para-aortic nodes. All patients were prescribed 45 Gy with 1.8 Gy per fraction to the pancreatic bed and regional lymphatics.

All patients received concurrent fluorouracil chemotherapy. The fluorouracil was administered by protracted venous infusion beginning on day 1 and continuing until completion of radiotherapy. The dose of fluorouracil protracted venous infusion was 250 mg/m² per day, 7 days per week. In the event of moderate or severe treatment-related toxic effects (grade ≥3), fluorouracil infusion was discontinued (for 3-7 days) and then resumed with a 10% to 20% dose reduction.

The National Cancer Institute Common Toxicity Criteria Scale was used to score the toxic effects from the adjuvant chemoradiotherapy. Each symptom is graded on a scale from 0 to 5 (in general representing none, mild, moderate, severe, life-threatening/disabling, or death) in reference to the patient’s prechemoradiotherapy symptoms. Patients were assessed twice a week during therapy.

Survival was calculated using Kaplan-Meier statistics from the date of surgery. Follow-up was updated in April 2000.

Medical Center for presumed carcinoma of the ampulla of Vater. Twelve patients were determined to have features of high-risk failure. The size of the tumor ranged from 1.5 to 3.0 cm (mean, 2.0 cm). Involvement of regional lymph nodes was documented in 10 patients. Patient characteristics are described in Table 1.

Twelve patients elected to receive adjuvant chemoradiotherapy and completed the prescribed treatment course. One patient required outpatient intravenous hydration, intravenous antiemetic drug therapy, and a treatment interruption of 7 days secondary to grade III nausea/vomiting. No other grade III, IV, or V toxic effects were noted. Grades I and II toxic effects observed consisted of nausea/vomiting, diarrhea, mucositis, and fatigue.

Median follow-up of surviving patients was 24 months (range, 13-50 months). Nine patients were alive at follow-up ranging from 13 to 50 months. Eight patients were disease free at the time of last follow-up. One patient who had recurrence in regional lymph nodes and in her lung remained alive at 50 months. Three patients died of this disease. All 3 patients who died developed liver metastases (one of these patients also developed a solitary lung lesion). Actuarial overall survival demonstrates a median survival of 34 months, 2-year survival of 89%, and 3-year survival of 44% (Figure). Median and overall actuarial survival for these patients was better than that in a parallel group of patients (n=26) with unfavorable features of primary pancreatic cancer who were resected, evaluated, and treated with the same adjuvant chemoradiotherapy regimen at Stanford University Medical Center (34 vs 14 months; P<.004) (Figure). One of 5 patients with ampullary cancer and favorable features failed locally 8 months after surgical resection. She is now receiving salvage chemotherapy. The other 4 patients were disease free at follow-up ranging from 10 to 28 months.

During the years, there have been improvements in the survival rate after radical resection of carcinoma of the ampulla of Vater. During the past decade, reports of 5-year survival have ranged from 20% to 61%, averaging more than 35% (Table 2). Carcinoma of the ampulla of Vater is generally thought to have better outcomes than true pancreatic primary malignancies. However, these series are retrospective and represent a selected population of patients with more favorable features.

Patients with unfavorable features (lymphovascular invasion, lymph node involvement, poor differentia-
tion, and involved surgical margins) tend to do much worse. In a large retrospective series from the Mayo Clinic, Rochester, Minn, evidence of lymphovascular invasion conferred a poorer prognosis, with median survival of 20.4 months (compared with 39.6 months for patients without evidence of lymphovascular invasion; \( P = .005 \)). Results of many series have confirmed that involvement of lymph nodes confers a much poorer prognosis, with 5-year survival ranging from 0% to 50% (Table 3). In the Mayo series, even involvement of a solitary lymph node conferred an equally poor prognosis to multiple involved lymph nodes, which suggests that the presence rather than the extent of nodal involvement is prognostic. In a large retrospective review from Memorial Sloan-Kettering Cancer Center, New York, NY, evidence of involved surgical margins predicted poor survival (11.3 vs 59.5 months; \( P < .02 \)) using multivariate analysis. Results of many series have confirmed that survival is affected by tumor grade.

There have been sporadic studies of adjuvant radiotherapy after pancreaticoduodenectomy. Willett and colleagues first reported on adjuvant radiotherapy for high-risk tumors of the ampulla of Vater (including invasion into the pancreas, poor differentiation, involved lymph nodes, or positive resection margins). Twelve patients received adjuvant radiotherapy (40.0-50.4 Gy) to the tumor bed, and some of these 12 received fluorouracil as a radiosensitizer. Compared with a group of 17 patients treated with surgical resection alone, there was a trend toward better local-regional control, but no advantage in overall survival was noted. The predominant failure pattern for patients treated with adjuvant radiotherapy was distant sites (liver, peritoneum, and pleura).

A recent EORTC (European Organisation for Research and Treatment of Cancer) trial randomized patients with pancreatic or periampullary cancer to observation or adjuvant radiotherapy (40 Gy, split course) and fluorouracil therapy after surgery. Forty-four patients with periampullary cancer (including distal common bile duct, ampulla of Vater, and duodenal) were randomized to receive adjuvant therapy. Only 14 patients in the periampullary group had nodal involvement. Only 31 of the 44 patients received the adjuvant treatment they were randomized to receive. Median (40 vs 40 months), 2-year (70% vs 51%), and 5-year (38% vs 36%) survival rates (by intent to treat), although appearing to modestly benefit adjuvant therapy, were not statistically significant.

The reported results of adjuvant chemotherapy after surgical resection for carcinoma of the ampulla of Vater are also limited. Barton and Copeland reported on the MD Anderson Cancer Center (Houston, Tex) experience of using postoperative chemotherapy for carcinoma of the ampulla of Vater. Seventeen patients received a variety of chemotherapeutic regimens (fluorouracil, doxorubicin, and mitomycin). This approach also did not seem to improve overall survival. In a retrospective review, Chan et al reported that 13 patients treated with adjuvant chemotherapy (involving predominantly fluorouracil, mitomycin, and doxorubicin) had a significantly better survival rate than did 16 patients who underwent surgical resection alone. Splinter et al found no difference in 3-year survival and local-regional control after curative resection with or without chemotherapy (fluorouracil, doxorubicin, and mitomycin). Bakkevold et al reported the results of the Norwegian Pancreatic Cancer Trial, which randomized patients to either observation or adjuvant chemotherapy (doxorubicin, mitomycin, and fluorouracil) after radical resection of carcinoma of the pancreas and ampulla of Vater. The treatment arm included 7 patients with completely resected carcinoma of the ampulla of Vater. Although the outcome for these patients was not reported, a small benefit of adjuvant chemotherapy in this patient population might be implied by the treatment arm demonstrating an improved median survival rate (23 vs 11 months; \( P = .02 \)). The survival benefit at longer time points (2 and 5 years) was not statistically different.

Yeung and colleagues used an interesting approach. They treated 20 patients with neoadjuvant chemoradiotherapy for presumed carcinoma of the head.

### Table 1. Characteristics of 12 Patients Who Underwent Adjuvant Chemoradiotherapy (1995-1999)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>66 (38-78)</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>7/5</td>
</tr>
<tr>
<td>Pancreatectoduodenectomy</td>
<td>12</td>
</tr>
<tr>
<td>Tumor size, mean (range), cm</td>
<td>2.0 (1.5-3.0)</td>
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<tr>
<td>Involved lymph nodes</td>
<td>10</td>
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<tr>
<td>Histological differentiation</td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>4</td>
</tr>
<tr>
<td>Moderate</td>
<td>5</td>
</tr>
<tr>
<td>Poor</td>
<td>3</td>
</tr>
<tr>
<td>Involved surgical margins</td>
<td>1</td>
</tr>
<tr>
<td>Neurovascular invasion</td>
<td>4</td>
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<tr>
<td>Tumor size ≥2 cm</td>
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<tr>
<td>Tumor stage</td>
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<td>T1</td>
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<tr>
<td>T2</td>
<td>11</td>
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<tr>
<td>T3</td>
<td>1</td>
</tr>
<tr>
<td>Survival, %</td>
<td></td>
</tr>
</tbody>
</table>

* Data are given as number of patients except where indicated otherwise.
of the pancreas, including 4 patients with duodenal/ampullary carcinomas. The 4 patients with radiographically defined duodenal/ampullary carcinomas all had a complete pathologic response to therapy, and all patients were alive at last follow-up.

Between 1995 and 1999, 17 patients underwent pancreaticoduodenectomy at Stanford University Medical Center for carcinoma of the ampulla of Vater. On review of pathologic findings, 12 patients were noted to have unfavorable features, including involved lymph nodes, involved surgical margins, neurovascular invasion, or poor histological differentiation. All of these patients elected to be treated on a protocol consisting of adjuvant chemoradiotherapy. Adjuvant chemoradiotherapy was well tolerated. At median follow-up of 2 years (range, 13-50 months), 9 of 12 patients were alive in this carefully selected population. Although 1 patient experienced a local-regional failure involving regional lymph nodes, the predominant failure pattern has been to the liver. Although our patient population had poor prognostic features, their survival is similar to that in other published series that included more favorable patients. The series of patients with high-risk features from the Massachusetts General Hospital, Boston,14 which includes patients most similar to our treated group, had 2-year survival of only 70% with surgery alone. In our series, 2-year actuarial overall survival for high-risk patients receiving adjuvant therapy is 89% (Figure). Five-year survival for patients with nodal involvement is 0% to 50% in published series (Table 2). This might suggest a possible benefit to an adjuvant chemoradiotherapy regimen. Compared with patients with true pancreatic malignancies (and unfavorable features), the survival rate seems to be better. The improved outcome compared with true primary pancreatic cancer suggests that ampullary carcinomas are a different (less malignant) and perhaps more responsive biologic entity. Our results are unique in that they represent what we think is the first effort to prospectively enroll patients with unfavorable carcinoma of the ampulla of Vater into a consistent adjuvant chemoradiotherapy regimen. Although the patient population is small (the disease is relatively uncommon), patients were accrued over a short time, evaluated with uniform criteria, and treated in a similar manner. A carefully designed, multi-institutional protocol is needed to more effectively define the role of adjuvant chemoradiotherapy in patients with unfavorable carcinoma of the ampulla of Vater.

**Corresponding author and reprints: Vivek K. Mehta, MD, Department of Radiation Oncology, Stanford University Medical Center, 300 Pasteur Dr, Stanford, CA 94305.**

**REFERENCES**

his prospective, controlled, single-arm study represents a valuable effort in justifying the need of adjuvant treatment in patients with ampullary carcinoma. Since the studies of the Gastrointestinal Study Group (GITSG), we have seen a significant increase in the use of adjuvant treatment for periampullary carcinomas, albeit with conflicting results. Although the 89% actuarial overall survival reported by Mehta et al is one of the highest reported, these data should be considered with caution, because of the small number of patients with limited follow-up. It should be noted that the median survival has not been reached in this group of patients due to limited follow-up and 3 deaths, although the authors reported the median survival to be 34 months. In addition, the authors compared these results with those of patients diagnosed as having pancreatic cancer; thus, one would expect to see differences in survival due to the inherently poor prognosis of patients with this disease.

In the current literature, there are a limited number of studies involving adjuvant therapy and ampullary cancer. There is only one large randomized and prospective trial involving adjuvant therapy in the treatment of cancers of pancreas and periampullary region, which was conducted by the EORTC. Although this study did not stratify for pure ampullary tumors, the 2-year survival rate for periampullary tumors was 63% in the observation group and 67% in the treatment group, and the 5-year survival rate was 36% vs 38%, with no statistical difference. Finally, Talamini et al reported a 28-year experience of the Johns Hopkins Hospital in which patients were treated with a similar adjuvant therapy that had no discernible influence on survival. Mehta and colleagues are to be commended for their study; however, the benefit of adjuvant therapy in this setting is yet to be determined. Larger randomized trials are needed to fully answer this question.

Carlos Alberto Ramírez Alvarado, MD
Selwyn M. Vickers, MD
Birmingham, Ala