What Prognostic Factors Are Important in Duodenal Adenocarcinoma?

Faisal G. Bakaeen, MA, MB, BCh; Michel M. Murr, MD; Michael G. Sarr, MD; Geoffrey B. Thompson, MD; Michael B. Farnell, MD; David M. Nagorney, MD; David R. Farley, MD; Jon A. van Heerden, MD; Lisa M. Wiersema, MD; Cathy D. Schleck, BS; John H. Donohue, MD

Hypothesis: Survival of patients with adenocarcinoma of the duodenum depends on the ability to perform a complete resection and the tumor stage.

Design: Retrospective case series.

Setting: Tertiary care referral center.

Patients: A cohort of 101 consecutive patients (mean age, 62 years), undergoing surgery for duodenal adenocarcinoma from January 1, 1976, through December 31, 1996. Patients with ampullary carcinoma were specifically excluded. Mean duration of follow-up was 4 years.

Interventions: Surgery was curative in 68 patients (67%) and palliative in 33 patients (33%). Of the curative group, 50 patients (74%) underwent radical surgery, ie, 30 (60%), pancreaticoduodenectomy; 15 (30%), pylorus-preserving pancreaticoduodenectomy; and 5 (10%), total pancreatectomy. A more limited resection procedure was used in 18 patients (26%) involving a segmental duodenal resection in 15 (83%) and a transduodenal excision in 3 (17%).

Main Outcomes and Measures: Tumor recurrence, patient survival, and correlation with patient and tumor variables using univariate and multivariate analysis.

Results: Actuarial 5-year survival for the curative group was 54%. Only 1 patient in the unresected group survived beyond 3 years. Nodal metastasis (P = .002), advanced tumor stage (P < .001), positive resection margin (P = .02), and weight loss (P < .001) had a significant negative impact on survival in multivariate analysis. Tumor grade, size, and location within the duodenum had no impact on survival. Patient age and tumor depth of invasion influenced survival in univariate analysis, but lost their prognostic significance in multivariate analysis.

Conclusions: Metastasis to lymph nodes, advanced tumor stage, and positive resection margins are associated with decreased survival in patients with duodenal adenocarcinoma. An aggressive surgical approach that achieves complete tumor resection with negative margins should be pursued. Pancreaticoduodenectomy is usually required for cancers of the first and second portion of the duodenum. Segmental resection may be appropriate for selected patients, especially for tumors of the distal duodenum.

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HE PROGNOSTIC IMPOR- TANCE of various demographic and histopathological factors in duodenal adenocarcinoma has been a subject of controversy in the literature. Nodal metastases, margins of resection, and depth of invasion, although of definite prognostic importance in many malignant neoplasms, have not consistently been shown to be of prognostic significance in duodenal adenocarcinoma. By virtue of the unique anatomy of the duodenum, the role of other factors such as tumor location and type of resection is also uncertain. These considerations are not surprising, since duodenal adenocarcinoma is a rare malignant neoplasm representing approximately 0.3% of all gastrointestinal tract cancers.1,2 Hence, many previous studies were limited by small patient numbers, prompting recent efforts to address this problem using larger cohorts.3-5 To better define the correlation between clinical, pathological, and treatment variables and outcome in patients with duodenal adenocarcinoma, we analyzed our institutional experience over a 20-year period.

RESULTS

DEMOGRAPHICS

Of the 101 patients, 51 were men and 50 were women. Patient age ranged from 31 to 100 years (median, 61 years). Eight patients had duodenal adenocarcinoma as-
PATIENTS AND METHODS

The records of all patients with duodenal adenocarcinoma who underwent surgery at the Mayo Clinic, Rochester, Minn, from January 1, 1976, through December 31, 1996, were reviewed. For patients to be included in this study, the surgeon and the pathologist had to agree that the primary tumor location was the duodenum. Special care was taken to exclude ampullary adenocarcinomas arising from the papilla of Vater. Patients with benign lesions and malignant neoplasms other than adenocarcinoma were excluded. A total of 101 patients fulfilled the inclusion criteria.

Demographics, clinical presentation, and diagnostic data were collected from the patients’ records. Pathological specimens were reviewed by one of us (L.M.W.) to confirm the diagnosis. Pathological data collected included resection margin, tumor grade, and tumor diameter. Tumor depth, nodal status, and metastasis were used in tumor staging as defined by the American Joint Committee on Cancer for malignant neoplasms of the small intestine.6

Sixty-eight patients (67%) underwent resection with curative intent, whereas the remaining 33 (33%) underwent a palliative operative procedure or open biopsy only. Types of resection included segmental resection, transduodenal excision, pancreaticoduodenectomy (PD), pylorus-preserving pancreaticoduodenectomy (PPPD), and total pancreatectomy (TP). The latter 3 operations were considered radical in nature for the purpose of our analysis. Survival data, including morbidity and mortality, were compiled. Follow-up to death or June 1998 was completed by using data from the Mayo Clinic Tumor Registry or telephone interviews using the Survey Research Center. Follow-up was complete for 99 patients (98%).

Actuarial survival curves were calculated by the Kaplan-Meier method.7 Differences in survival were determined by the log-rank test. Multivariate comparisons were performed using the Cox proportional hazards model.8 Differences between resection groups were evaluated by χ² analysis, Wilcoxon rank sum test, and Fisher exact test as appropriate (P≤.05 was considered significant in all tests). Data are presented as median values or as mean ± SEM, as appropriate.

DIAGNOSIS

A range of preoperative diagnostic studies were performed in these patients (Table 1). Upper gastrointestinal tract endoscopy, the most frequently performed test, failed to identify the tumor in 7 of 84 patients undergoing the study. In these 7 patients, upper gastrointestinal tract radiography (6 patients) and computed tomography (1 patient) subsequently identified the tumor. Four of these patients had tumors in the third (D3) or fourth (D4) portion of the duodenum. Forty-seven patients underwent endoscopic biopsies, among which 41 specimens (87%) were positive for adenocarcinoma.

OPERATIVE TREATMENT

Of the 68 patients undergoing curative resections, 30 (44%) had a PD; 15 (22%), a PPPD; 5 (7%), a TP; and 18 (27%), a limited resection. Limited resection included 15 (83%) segmental duodenal resections and 3 (17%) transduodenal excisions (Table 2). Three patients among the resected group had an initial palliative bypass elsewhere and subsequently underwent a curative resection at our institution.

Among the palliative group, 10 adenocarcinomas (30%) were deemed unresectable because of local invasion of the retroperitoneum or visceral vascular involvement, whereas the remaining 23 patients (70%) had distant metastatic disease. Thirty (91%) of the palliative group had a bypass procedure. The remaining 3 patients underwent open biopsy only. Two of these had had a palliative bypass at another institution before presenting at our institution.

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>No. (%) of Patients</th>
<th>Location in Duodenum, No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection</td>
<td></td>
<td>D1 D2 D3 D4</td>
</tr>
<tr>
<td>Pancreaticoduodenectomy</td>
<td>45 (45)</td>
<td>1 27 2 0</td>
</tr>
<tr>
<td>Classic</td>
<td>30 (30)</td>
<td>1 0 0 0</td>
</tr>
<tr>
<td>Pylorus-preserving</td>
<td>15 (15) 0 0 0</td>
<td></td>
</tr>
<tr>
<td>Total pancreatectomy</td>
<td>5 (5)</td>
<td>0 0 0 0</td>
</tr>
<tr>
<td>Limited resection</td>
<td>18 (18) 1 2 6 6</td>
<td></td>
</tr>
<tr>
<td>Segmental duodenal resection</td>
<td>15 (15)</td>
<td>1 2 6 6</td>
</tr>
<tr>
<td>Transduodenal excision</td>
<td>3 (3)</td>
<td>1 2 0 0</td>
</tr>
<tr>
<td>Palliative or biopsy</td>
<td>33 (33)</td>
<td>1 5 3 1</td>
</tr>
<tr>
<td>Locally advanced disease</td>
<td>10 (10)</td>
<td>1 14 3 5</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>23 (23)</td>
<td>1 14 3 5</td>
</tr>
</tbody>
</table>

* χ² indicates first portion; D2, second portion; D3, third portion; and D4, fourth portion of the duodenum.

Table 1. Preoperative Diagnostic Studies Used and Accuracy for Duodenal Adenocarcinoma

<table>
<thead>
<tr>
<th>Study</th>
<th>All (%)</th>
<th>Diagnostic (%)</th>
<th>Non-diagnostic (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopy</td>
<td>84 (83)</td>
<td>77 (92)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Upper gastrointestinal tract radiography</td>
<td>61 (60)</td>
<td>55 (80)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Computed tomography</td>
<td>53 (52)</td>
<td>42 (79)</td>
<td>11 (21)</td>
</tr>
</tbody>
</table>

* Of total N = 101.
MORBIDITY AND MORTALITY

One patient died, for an overall in-hospital mortality of 1%. This 60-year-old woman underwent a PPPD complicated by a biliary anastomotic leak, sepsis, coagulopathy, and hemorrhage. Among the palliative group, 1 or more postoperative complications developed in 12 patients (36%). Forty-one patients (60%) of the resection group suffered 1 or more complications. The complication rates were not significantly higher in those undergoing radical vs limited resection (32 patients [64%] vs 24 patients [73%]); P = .30. Leakage from the pancreatic anastomosis complicated 7 PD and PPPD (16%). Biliary anastomotic leak occurred in 5 radical resections (10%). The median postoperative length of stay was 10.5 days for the palliative group and 15 days for the curative group (P = .007). The median duration of hospitalization after radical surgery was 18 days and after limited resection was 9.5 days (P < .001).

PATHOLOGICAL FINDINGS

In the patient cohort undergoing curative resection, mean tumor diameter was 4.0 (±1.9) cm. Fifty tumors (74%) were in the second portion of the duodenum (D2), with more than half of these (36/68 [53%]) periampullary. The other duodenal adenocarcinomas were distributed as follows: 9 (13%) in D3, 6 (9%) in D4, and 3 (4%) in the first portion of the duodenum (D1). Ten tumors (15%) arose within a villous adenoma. Results of histological examination of margins were negative in 60 patients (88%) and positive in 8 patients (12%). Sixty-one patients (60%) had tumors that were well to moderately differentiated, with the tumors of the remaining 40 patients (40%) being poorly differentiated. The TNM staging of tumors is summarized in Table 3.

ADJUVANT TREATMENT

After curative resection, 17 patients (25%) in the resected group underwent adjuvant postoperative external beam irradiation with fluorouracil chemosensitization. One patient also underwent intraoperative irradiation because of a positive resection margin. The tumor bed radiation dose ranged from 4500 to 5600 cGy. One patient received leucovorin calcium in addition to fluorouracil, and 2 other patients received additional systemic chemotherapy at other institutions. Statistical analysis failed to identify any impact of chemoradiation on patient survival (P = .40) or cancer recurrence (P = .14), although such a statistical analysis should be interpreted with caution.

SURVIVAL

Mean overall patient follow-up was 4.0 ± 4.8 years (median, 2 years). Overall actuarial survivals at 3 and 5 years for all 101 patients were 43% and 37%, respectively. The resection group had a mean follow-up of 5.5 ± 5.2 years (median, 3.3 years). Patients with resectable tumors had actuarial 3- and 5-year survival rates of 61% and 54%, respectively. Only 1 patient in the palliative group survived beyond 3 years (Figure 1). Two patients in the resection group had distant metastases at the time of diagnosis. One had a solitary hepatic metastasis in the right lobe of the liver discovered at exploration and treated with a wedge resection concomitantly with PPPD. He died just more than 5 years after surgery. The second patient had an abnormality involving the T11 vertebra believed to be indeterminate during preoperative evaluation. Because of symptoms, he underwent exploration and resection, but the vertebral lesion proved malignant on results of a postoperative needle biopsy. This patient died 4 months later.

PROGNOSTIC VARIABLES

In the resected group, univariate analysis showed that older age, weight loss, nodal metastases, positive margin, depth of invasion, and advanced tumor stage were associated with decreased survival (P≤.06) (Table 4). Tumor grade, diameter, and location within the duode-
num had no significant impact on survival. When subjected to multivariate analysis, patient age and depth of invasion lost significance when correlated to survival, whereas nodal metastases, positive margins, and stage were significant prognostic predictors (Table 4). The 3- and 5-year actuarial survival rates of patients with negative nodes were 73% and 68%, respectively, compared with 35% and 22% in patients with nodal metastases (Figure 2). The 3- and 5-year actuarial survival rates were 64% and 58%, respectively, for patients with clear pathological margins vs 38% and 25% in patients with positive margins (Figure 3). Patients with stages III and IV cancer had lower survival rates compared with patients with less advanced cancers (Figure 4).

### RADICAL VS LIMITED RESECTION

The extent of resection did not affect survival (Figure 5). The radical and limited resection groups were similar for patient and tumor variables except for tumor location and size. Forty-six (92%) of the 50 tumors of the second portion of the duodenum underwent radical resection ($P<.001$) (Table 5). Tumors in the radical surgery group (median diameter, 4.0 cm) were larger than those in the limited resection group ($P<.001$) (Table 5). Tumors in the radical surgery group (median diameter, 4.0 cm) were larger than those in the limited resection group ($P<.001$).

#### Table 4. Variables Influencing Survival in Patients Undergoing Resection for Duodenal Adenocarcinoma

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>.004</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stage†</td>
<td>.004</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nodal metastases</td>
<td>.003</td>
<td>.002</td>
</tr>
<tr>
<td>Positive margins</td>
<td>.06</td>
<td>.02</td>
</tr>
<tr>
<td>Depth of invasion‡</td>
<td>.009</td>
<td>.20</td>
</tr>
<tr>
<td>Age</td>
<td>.05</td>
<td>.28</td>
</tr>
<tr>
<td>Tumor grade</td>
<td>.17</td>
<td>.§</td>
</tr>
<tr>
<td>Diameter of tumor</td>
<td>.85</td>
<td>.§</td>
</tr>
<tr>
<td>Location of lesion</td>
<td>.97</td>
<td>.§</td>
</tr>
<tr>
<td>Type of resection</td>
<td>.79</td>
<td>.§</td>
</tr>
<tr>
<td>Chemoirradiation</td>
<td>.40</td>
<td>.§</td>
</tr>
</tbody>
</table>

*Significant P values are indicated with boldface type.
†Stages III and IV tumors were grouped together as a single variable in the multivariate analysis. This analysis model did not include nodal metastases to avoid overlap of variables (ie, stage III and nodal metastases).
‡Tumor limited to duodenal wall vs transmural and adjacent organ invasion, shown in Table 2.
§Ellipses indicate variables for which multivariate analysis was not performed because of nonsignificant P values in univariate analysis.
limited resection group (median diameter, 3.0 cm) \( (P = 0.02) \). The number of patients with positive margins and the frequency of nodal metastases were not significantly different between the radical and limited resection groups. Both resection groups also had a similar incidence of patients with advanced tumor stage (Table 5). The median number of lymph nodes resected was 2 (range, 0-15) in the radical resection group \( (P = 0.002) \). Pancreatic insufficiency requiring dietary enzyme supplement and/or diabetes developed in 17 patients (34%) who underwent radical surgery, and diabetes was subsequently diagnosed in 2 patients (11%) who underwent limited resection \( (P = 0.07) \).

**TUMOR RECURRENCE**

Recurrence was found in 25 patients (37%). In 4 patients (16%), the site of recurrence was local only; in 10 (40%), local recurrence and distant metastases were documented; and the remaining 11 (44%) had distant failure only. The most common site of distant failure was the liver (15 patients [60%]). Median time to tumor recurrence was 1.3 years. Median survival of patients after the diagnosis of recurrent disease was 10.4 months. Univariate analysis demonstrated that only weight loss \( (P = 0.002) \) influenced overall recurrence. There was a trend toward reduced local recurrence with negative resection margins \( (P = 0.06) \). Chemoirradiation had no significant impact on local recurrence \( (P = 0.27) \).

**COMMENT**

We designed this study to address factors that influence the outcome for patients with duodenal adenocarcinoma. There has been a considerable controversy in the literature regarding prognostic indicators, likely because of the rarity of this malignant neoplasm and the small patient numbers in most published experiences. In our series of 101 patients, the 5-year actuarial survival rate was 54% for the 68 patients with resectable disease. Along with resectability, negative resection margins, absence of nodal metastases, and early tumor stage were significant predictors of improved survival. Weight loss was an indicator of poor outcome even after a potentially curative resection. Duodenal adenocarcinoma often presents with vague and nonspecific symptoms that lead to delayed diagnosis. Weight loss reflects a later stage in the natural history of the disease and would likely explain the negative prognostic impact. Other signs and symptoms, including pain, bleeding, or jaundice, had no demonstrable influence on survival.

There is general agreement that patients with resectable duodenal cancer achieve better survival than patients with unresectable tumors. Current 5-year survival rates range from 43% to 87%. Survival figures for patients undergoing resection have varied widely; however, our survival rate of 54% is comparable to that achieved in more recent and larger series \( (P = 0.27) \). In a previous experience reported from our institution, the resectability rate was 51%, and 5-year survival was 46%. Whether overall resectability rates will continue to improve with better preoperative staging and willingness to perform more aggressive surgery is unknown.

The optimal extent of resection for duodenal adenocarcinoma has not been well defined. Some authors advocate PD for all patients with adenocarcinoma of the duodenum, including those located in the D3 and D4, to ensure adequate en bloc resection. The value of routine extensive resections for nodal clearance has been recently challenged. Other groups support the use of PD for proximal duodenal carcinomas, but segmental resec-

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**Table 5. Type of Resection According to Location of Duodenal Cancer, Pathological Margin Involvement, Lymph Node Status, and Stage**

<table>
<thead>
<tr>
<th>Location</th>
<th>Local Resection</th>
<th>Radical Resection</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients, No.</td>
<td>(n = 18)</td>
<td>(n = 50)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Margin</td>
<td>Negative</td>
<td>60 (14)</td>
<td>46 (92)</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>8 (22)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Nodes</td>
<td>Negative</td>
<td>46 (13)</td>
<td>33 (66)</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>22 (58)</td>
<td>17 (34)</td>
</tr>
<tr>
<td>Stages III and IV</td>
<td>24 (52)</td>
<td>19 (38)</td>
<td>.44</td>
</tr>
</tbody>
</table>

*Percentages have been rounded and may not sum to 100.*

†Abbreviations are explained in the footnote to Table 2.

**Table 6. Published Results Including More Than 50 Patients With Duodenal Adenocarcinoma**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Resectability, %</th>
<th>Lymph Node Positive, %</th>
<th>5-Year Survival After Resection, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alwmark et al</td>
<td>1958-1973</td>
<td>66</td>
<td>43</td>
<td>...</td>
</tr>
<tr>
<td>Joesting et al</td>
<td>1937-1977</td>
<td>104</td>
<td>51</td>
<td>...</td>
</tr>
<tr>
<td>Rotman et al</td>
<td>1978-1988</td>
<td>66</td>
<td>71</td>
<td>37</td>
</tr>
<tr>
<td>Barnes et al</td>
<td>1967-1991</td>
<td>67</td>
<td>61</td>
<td>36</td>
</tr>
<tr>
<td>Saxe et al</td>
<td>1987-1991</td>
<td>85</td>
<td>44</td>
<td>...</td>
</tr>
<tr>
<td>Santoro et al</td>
<td>1980-1994</td>
<td>89</td>
<td>73</td>
<td>23</td>
</tr>
<tr>
<td>Rose et al</td>
<td>1983-1994</td>
<td>79</td>
<td>63</td>
<td>38</td>
</tr>
<tr>
<td>Sahn et al</td>
<td>1984-1996</td>
<td>55</td>
<td>87</td>
<td>56</td>
</tr>
<tr>
<td>Present study</td>
<td>1976-1996</td>
<td>101</td>
<td>67</td>
<td>32</td>
</tr>
</tbody>
</table>

*Ellipses indicate values not stated in the study cited.*

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tion for cancers of the D3 and D4.5,9,10,11 No adverse effect on survival has occurred with a more localized extirpation. This might not be unexpected, because much of the lymphatic drainage of these distal portions of the duodenum is into the small bowel mesentery and not via the pancreaticoduodenal lymphatic basins removed by a PD. In our series, there was no demonstrable difference in 5-year survival between patients undergoing radical resection (52%) and segmental resection (61%). Although there was a trend toward an increased incidence of local recurrence with the limited resection cohort compared with the radical resection group (P = .12), there was no difference in the incidence of clear pathological margins between both types of procedures. If a negative resection margin can be secured, the type of surgical procedure appears of lesser importance in distal duodenal cancers, because neither segmental nor radical resection can remove the draining nodal basin.

There are circumstances when PD may be more prudent than segmental resection. In patients with FAP, the entire duodenal mucosa is at risk. Patients with large or periampullary cancers, in whom it would be technically difficult to perform a lesser procedure without compromising resection margins, require a PD. Transduodenal resection is an inadequate operation for invasive duodenal carcinoma. This procedure carries a significant risk for recurrence. Our own experience has shown that transduodenal local excision of villous adenomas of the duodenum leads to 30% local failure.16 In the past, a Whipple procedure was considered to have prohibitive morbidity and mortality risks; however, many institutions have reported a significant improvement in perioperative complications.17-21 In our patients, the complication rate was comparable between the radical and limited resection groups, but the length of hospitalization was longer following larger procedures.

Nodal metastases have been associated with poor prognosis by previous investigators.9,22 Recently, other groups have reported no significant impact of nodal status on survival.3,4,22 In our series, nodal metastases were clearly associated with decreased survival (68% vs 22%), but did not preclude cure. The median number of nodes in the resected specimen was higher in the radical surgery group (6 nodes) compared with the limited resection group (2 nodes). Despite potential downsizing in the limited resection group, no difference in survival was noted when compared with the radical resection group.

Significant differences in survival occurred by tumor stages, as demonstrated in Figure 4. Both patients with stage 0 cancer achieved 100% long-term survival, and both with stage IV cancer were dead at just more than 5 years. In multivariate analysis, patients with stages 0, I, and II disease had improved survival compared with patients with stages III and IV disease (P < .001). This is not surprising since, as with other cancers, patients with nodal and distant metastases have diminished survival.

Our study, in agreement with another report,4 demonstrated no difference in survival based on the location of the cancer in different portions of the duodenum. Two other studies reported improved survival with more distal duodenal tumors,2,17 whereas a third experience3 demonstrated better outcome with proximal duodenal malignant neoplasms. Patient selection and stage probably account for those differences.

In most patients whose disease recurred, the initial pattern included distant failure. There were no defined criteria for offering adjuvant chemoirradiation therapy to patients, and the delivered treatment was variable. We fully acknowledge the lack of controlled data to support its use as an adjuvant therapy. We also cautiously report our inability to demonstrate a survival benefit of such treatment, but emphasize that the statistical analysis suffers from many limitations (nonrandomized, potential selection bias, and inadequate numbers), precluding reliable analysis.

**CONCLUSIONS**

Long-term survival for patients with duodenal adenocarcinoma can be achieved with a surgical procedure that produces negative resection margins. Pancreatectoduodenectomy likely is required to achieve this goal for most lesions in the D1 and D2. Segmental resection is appropriate for select patients, especially with lesions of the distal duodenum. Metastatic nodal involvement, advanced tumor stage, and preoperative weight loss predict poorer patient survival but do not preclude cure. Some form of effective adjuvant systemic therapy is needed for this malignant neoplasm, given the high distant failure rate after curative resection.

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Reprints: John H. Donohue, MD, Department of Surgery, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (e-mail: donohue.john@mayo.edu).

**REFERENCES**

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DISCUSSION

Gerard V. Aranha, MD, Maywood, Ill: This is the Mayo Clinic, and is a report of 101 patients. Combine that with the 104 patients that they presented in a report in 1977 by Drs Joesting, van Heerden, and Weiland, and they have the largest series of such patients in this country.

Dr Bakaeen has made an excellent presentation telling us what factors influence survival in duodenal adenocarcinoma and that we should be aggressive surgically, that is, to obtain negative margins. Even if nodes are positive, there is an appreciable 5-year survival, supporting further the need to be aggressive.

Now there is no doubt that we are going to see more of these tumors. The increasing application of upper GI [gastrointestinal] endoscopy for vague upper GI complaints and the recognition that these tumors are associated with FAP, I think, will result in an increase in the diagnosis of these tumors.

You say, be more aggressive. Should we do a Whipple for all 4 areas of the duodenum? You said that you would do a Whipple for the proximal D1 and D2 lesions, but for the distal lesions you would do a segmental resection. Will that strategy remain in your practice? And, if you see these tumors in patients who have FAP or the other preexisting conditions like strue or Crohn's, would you apply the same strategies?

What is your current practice in relation to villous adenomas of the duodenum? You didn’t talk about pancreas invasion. If you look at ampullary carcinoma and bile duct carcinoma, the invasion of the pancreas connotes a bad survival. Did you look at that? There is a Japanese report suggesting that duodenal adenocarcinoma with invasion of the pancreas has a poor prognosis.

And finally, I suppose that all clinical papers deserve some speculation. You have talked about positive margins and positive nodes being bad, but you had about the same proportion in each group, whether there was a limited resection or aggressive resection. If you look at your failure rate, 80% of your failures are distant. So what is important here, the aggressiveness of the surgeon or the biology of the tumor? What strategies do you have to combat the biology of these tumors?

Richard A. Prinz, MD, Chicago, Ill: I was intrigued that you did limited resections for tumors in the first, second, and even, it seemed, the proximal third part of the duodenum. Can you share with us your thoughts on when it is appropriate to do limited resections in these locations? Do you utilize endoscopic ultrasound (EUS) in any way to evaluate tumor invasion in this area? You also performed 5 total pancreatectomies in this series. I wondered what were the indications for that procedure. Finally, you could only do a palliative procedure in a substantial number of patients. Could you share with us what is the best palliation for these patients? This is especially important in this day, when our interventional colleagues can put stents through these tumors and keep these patients eating.

Jack Pickleman, MD, Maywood: I hate to follow Dr Aranha on the podium because this might be construed as some sort of a Jesuit plot, but a couple of years ago we published our series of duodenal adenocarcinomas and we made the point that node positivity, although an adverse factor, was still comparable with cure, and we have updated that series of patients prior to this meeting. Four of those patients who had multiple nodes positive are still alive and well. I am concerned about the mixed message that I am getting on this paper. Message number 1 is, be radical. Message number 2 is, do segmental resections. I am not sure you can have it both ways. There must be a cohort of patients with cancer of the third and fourth portions of the duodenum who would be better served by radical resection, a Whipple procedure in continuity with a radical nodal dissection, rather than just a segmental resection.

Theodore X. O'Connell, MD, Los Angeles, Calif: I have several questions. The first one is, since 75% of the cases occurred in the second portion of the duodenum, how many of these are ampullary carcinomas presenting with jaundice, etc, rather than typical duodenal carcinoma? The second question regards the radical surgery. I don’t know if it is right to say radical vs not radical surgery. You do the surgery depending on where the tumor is. In your conclusion, you say that the D3 and the D4 tumors should be treated by segmental resection and the D1s and D2s, by radical resection. However, what are the data to substantiate that from the paper? Also, why shouldn’t a proximal D1 at the area of the pylorus be also treated by a local segmental resection, just like you would a D3 or a D4?

Frederic E. Eckhauser, MD, Ann Arbor, Mich: I have 2 questions. The first relates to the author’s comments about limited resection. The authors didn’t provide any comparative survival or recurrence data relative to whether they had performed limited vs radical resections. I wonder if they would amplify that during the discussion.

Second, there was a very disturbing recurrence rate, which I calculated to be about almost 60%. By convention, most duodenal or peripanillary cancers are not treated with adjuvant chemoradiation therapy, because the biological behavior of the tumors is such that survivals at 5 years and longer probably exceed 50% to 60% in most series. Did the authors feel that their data would justify the routine use or consideration of adjuvant chemoradiation therapy for all of these patients as has become the standard for ductal adenocarcinoma of the pancreas?

Lawrence W. Way, MD, San Francisco, Calif: What useful lessons do you think can be drawn from these data? Perhaps one would be that outcomes might have been better if positive margins could have been avoided. If so, can changes be made in operative management that would improve the results? For example, under what circumstances did positive margins occur? Did positive margins come as a surprise, or were they the best possible compromise in certain operations? Could something be done to avoid positive margins? Should frozen-section examinations be done as a routine?

Second, do you have recommendations on how to treat a patient whose principal manifestation is bleeding but whose
tumor is unresectable? Have you found ways to control the bleeding short of removing the tumor?

James A. Schulak, MD, Cleveland, Ohio: My question is very similar to Dr Way’s regarding positive margins. Could the authors tell us whether or not they were more likely to have positive margins with pyloric-preserving procedures rather than the classical Whipple, and, if so, is that operation an appropriate operation for a bowel cancer that lies within several centimeters of the proposed margin?

Dr Donohue: A number of questions arise, some of them variations on a theme. A lot of them addressed differences between limited and radical resection. A question from Dr Aranha echoed by others was should a Whipple procedure be performed for cancers of the third and fourth portions of the duodenum? If there is direct involvement of the pancreas, a radical operation would be our practice. However, many of these patients did not have T4 tumors. The problems for distal duodenal cancer cure include lymph node spread along the superior mesenteric vessels and direct involvement of the superior mesenteric vessels. A standard pancreaticoduodenectomy will not improve survival in these instances. There is a role for segmental resection in patients with localized distal duodenal cancers.

Dr Aranha questioned whether patients with FAP, celiac sprue, and other predisposing causes should be treated more aggressively. There were 8 patients with FAP in this series, all of whom were treated with a pancreaticoduodenectomy. All of them had tumors in the periampullary region; their treatment was similar to patients without a predisposing etiology.

Dr Aranha also asked about our management of villous adenomas. Dr Farnell, a coauthor and member of this society, recently looked at our experience with duodenal villous adenomas. Our usual practice has been local excision of these tumors, but Dr Farnell found a 30% local recurrence rate with this practice. Can more radical treatment, such as PPPD, lower these rates? This is a question for future study.

Dr Aranha also asked about the direct involvement of the pancreas as a prognostic variable. T4 tumors comprised 28% of the curative group. T4 status was not a significant prognostic factor in multivariate analysis.

Lastly, Dr Aranha asked about improving outcome with more aggressive surgery. The majority of patients whose disease recurred had a component of distant failure. There is a limit to the extent of resection feasible, and we are near that point. The natural history of this disease kills most patients who recur. A form of effective adjuvant therapy is needed to best improve overall survival rates.

Dr Prinz asked a question about limited resection. We do not routinely perform a limited resection, but for a localized cancer in the distal third and fourth portions, where the duodenum is distinct from the pancreas, a segmental resection has a role as a curative procedure.

Dr Prinz asked about the use of endoscopic ultrasound (EUS). Only 2 patients in this time frame had EUS. Our gastroenterologic colleagues are now routinely performing EUS, trying to better stage tumors preoperatively.

Dr Prinz asked about the indications for TP. For the 5 patients in this cohort having TP, the quality of the pancreatic tissue was such that it did not allow an adequate enteric anastomosis. Total pancreatectomy would also be used in patients who have preexisting diabetes mellitus.

Dr Prinz asked about our palliative procedures. All but 3 patients underwent a gastric bypass and most with proximal duodenal cancers had a biliary bypass. Of the 3 patients who did not have a bypass, 2 had already undergone bypass before referral to our institution.

Dr Pickleman also asked a question about pancreaticoduodenectomy being better for distal duodenal tumors. I believe I have addressed this issue in answering Dr Aranha’s questions.

Dr O’Connell questioned whether there were any ampullary tumors in this experience. Our reason for pathological review of all operative specimens was to exclude any patient with an ampullary carcinoma. He also asked about local resection for a cancer of the first portion of the duodenum, much like segmental resection in the distal duodenum. For in situ cancers, T1 lesions and perhaps selective T2 carcinomas, this approach might be considered. These are very rare cancers.

Dr Eckhauser asked about survival differences between the limited and radical resection groups. Patient treatment was not performed in a controlled fashion. The outcome results for these 2 groups were similar.

Dr Eckhauser questioned the high incidence of local recurrences. Local recurrence alone was uncommon. None of the 4 patients with an isolated local recurrence, which included any failure within the operative bed, thereby including regional or nodal recurrences, had positive resection margins.

In response to his question about adjuvant treatment, chemoradiation therapy was delivered postoperatively in 25% of the patients undergoing curative resection in an uncontrolled fashion. There was no statistical effect on survival, but this is an uncontrolled retrospective experience. Chemoradiation therapy should be considered for patients at high risk for recurrence; however, no data to prove benefit in duodenal cancer exist.

Dr Way asked about what we have learned in terms of trying to avoid positive margins. Frozen-section analysis is routine at Mayo Clinic, whether the operative procedure is a duodenal resection, breast cancer operation, or most any other procedure. Some of the positive margins were identified at the time of resection. In patients where involvement around the superior mesenteric vessels was noted, no further resection was performed. There were positive margins at the pancreatic resection line or in the retroperitoneum that could be addressed by wider excision.

Dr Way also asked about palliation of a bleeding unresectable duodenal cancer. This is a very difficult problem in a patient with a short life expectancy. A palliative resection should be considered in selected patients. Embolization and other nonoperative techniques are unlikely to be useful in these patients. Only 20% of our entire patient population had bleeding that was recognized clinically.

Lastly, Dr Schulak asked me if positive resection margins occurred more often with a PPPD vs a classic Whipple procedure. There was no evidence in this experience to suggest more frequent positive margins with any of the radical resectional procedures.