Hypothesis: In patients with duodenal adenocarcinoma, certain pathologic features of the tumor will have prognostic significance.

Design: Retrospective case series.


Results: The tumors of 31 (63%) of the 49 patients underwent resection, 18 (37%) had surgical palliation or underwent biopsy. Mean (±SEM) survival for all patients was 49±9 months. The patients whose tumors were resected had longer survival than those who underwent palliation (mean±SEM, 66±13 months vs 18±6 months, \( P = .02 \)). Multivariate analysis revealed large tumor size (\( P = .01 \)), transmural invasion (\( P = .004 \)), and moderate to poor tumor grade (\( P = .03 \)) were negatively correlated with survival. Lymph node status did not influence survival.

Conclusions: Our 40-year experience with duodenal adenocarcinoma demonstrates that large tumor size, advanced histological grade, and transmural invasion are associated with decreased survival. These results underscore the importance of early diagnosis, and suggest the presence of nodal spread is not a contraindication to resection.

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PATIENTS AND METHODS

The medical records of 49 patients with a microscopic tissue diagnosis of duodenal adenocarcinoma treated at University of California Los Angeles (UCLA) Medical Center between March 1, 1957, and May 11, 1998, were reviewed. Follow-up data were obtained from the UCLA Cancer Registry Center and through contact with the patients’ personal physicians. Review included patient demographics (age, sex, race, date of diagnosis); data regarding the surgery (type of surgery, duration, estimated blood loss, blood transfused, and perioperative complications); tumor characteristics (location, size, degree of differentiation, invasion of surrounding structures, lymph node status, and metastatic disease); and use of adjuvant chemotherapy or radiotherapy.

With one of us performing statistical validation, a multiple regression analysis was done to determine which study factors were associated with patient survival. The initial selection of variables was intuitive, based on apparent clinical relevance, so as to limit the number of predictors. Then stepwise linear regression was performed to finalize the regression model. All analyses were done with Stata software (College Park, Tex). Statistical significance was rated at P<.05. Wherever appropriate, data are presented as mean±SEM.

OPERATIVE CHARACTERISTICS

The tumors of 31 (63%) of the 49 patients underwent potentially curative resection, the remaining 18 (37%) had a palliative bypass or underwent biopsy only. Unresectable lesions were characterized by involvement of large blood vessels (ie, inferior vena cava, aorta, superior mesenteric artery or vein), extensive retroperitoneal invasion, and/or distant metastasis. Of the 31 patients whose tumors were resected, 27 (88%) had microscopically clear margins. For all patients who were operated on, the estimated mean blood loss was 792±127 mL, the mean number of units transfused was 1.25±0.3, the average length of the surgery was 6.0±0.4 hours, and the average length of hospital stay was 24±2 days. Two perioperative deaths (4%) (defined as deaths during the hospital stay in which the operation was performed) occurred. Both of these patients had undergone pancreaticoduodenectomy. Postoperative complications occurred in 23 (48%) of the patients and included wound infection (3 patients), intraabdominal abscess (1 patient), pancreatic fistula (4 patients), gastrointestinal hemorrhage (2 patients), pulmonary embolus (1 patient), hepatic coma (1 patient), and prolonged ileus (12 patients).

Table 1. Comparison of Operative Characteristics

<table>
<thead>
<tr>
<th>Operative Characteristic</th>
<th>Overall (N = 49)</th>
<th>Patients Whose Tumor Was Resected (n = 31)</th>
<th>Patients Whose Tumor Was Not Resected (n = 18)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBL, mean ± SEM, mL</td>
<td>792 ± 127</td>
<td>1014 ± 186</td>
<td>376 ± 80</td>
<td>.02</td>
</tr>
<tr>
<td>Transfusion, mean ± SEM, U</td>
<td>1.25 ± 0.3</td>
<td>2.0 ± 0.5</td>
<td>0.2 ± 0.1</td>
<td>.009</td>
</tr>
<tr>
<td>Length of operative time, mean ± SEM, h</td>
<td>6.0 ± 0.4</td>
<td>7.3 ± 0.4</td>
<td>3.7 ± 0.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LOS, mean ± SEM, d</td>
<td>24 ± 2</td>
<td>25 ± 3</td>
<td>21 ± 3</td>
<td>.39</td>
</tr>
<tr>
<td>Perioperative morbidity rate, %</td>
<td>48</td>
<td>45</td>
<td>53</td>
<td>.16</td>
</tr>
<tr>
<td>Perioperative mortality rate, %†</td>
<td>4</td>
<td>6</td>
<td>0</td>
<td>.30</td>
</tr>
<tr>
<td>5-Year survival, %</td>
<td>33</td>
<td>43</td>
<td>13</td>
<td>.04</td>
</tr>
</tbody>
</table>

*EBL indicates estimated blood loss; LOS, length of hospital stay. †Perioperative mortality defined as death occurring during the initial hospitalization.

Table 2. Comparison of Patient Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Overall (N = 49)</th>
<th>Patients Whose Tumor Was Resected (n = 31)</th>
<th>Patients Whose Tumor Was Not Resected (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SEM, y</td>
<td>61.3 ± 1.6</td>
<td>60.3 ± 2.1</td>
<td>63.1 ± 2.5</td>
</tr>
<tr>
<td>Male</td>
<td>49</td>
<td>52</td>
<td>44</td>
</tr>
<tr>
<td>White</td>
<td>76</td>
<td>74</td>
<td>78</td>
</tr>
<tr>
<td>Received adjuvant therapy†</td>
<td>31</td>
<td>23</td>
<td>44</td>
</tr>
</tbody>
</table>

*Unless otherwise specified, all values expressed as percentages. †Adjuvant therapy includes patients receiving chemotherapy, radiotherapy, or both.
Table 3. Comparison by Period of Resection

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who underwent resection, No.</td>
<td>17</td>
<td>14</td>
<td>.1</td>
</tr>
<tr>
<td>EBL, mean ± SEM, mL</td>
<td>1315 ± 313</td>
<td>659 ± 126</td>
<td>.07</td>
</tr>
<tr>
<td>Transfusion, mean ± SEM, U</td>
<td>2.6 ± 0.8</td>
<td>1.2 ± 0.5</td>
<td>.10</td>
</tr>
<tr>
<td>Length of operative time, mean ± SEM, h</td>
<td>6.7 ± 0.5</td>
<td>8.0 ± 0.7</td>
<td>.11</td>
</tr>
<tr>
<td>LOS, mean ± SEM, d</td>
<td>30 ± 5.0</td>
<td>20 ± 3.0</td>
<td>.10</td>
</tr>
<tr>
<td>Perioperative morbidity rate, %</td>
<td>47</td>
<td>43</td>
<td>.90</td>
</tr>
<tr>
<td>Perioperative mortality rate, %‡</td>
<td>12</td>
<td>0</td>
<td>.19</td>
</tr>
</tbody>
</table>

*EBL indicates estimated blood loss; LOS, length of hospital stay.
†Ellipses indicate not applicable.
‡Perioperative mortality defined as death occurring during the initial hospitalization.

The 3 longest survivors (25%) survived 12 months, and 4 (25%) survived 16 months. In contrast, in the group of the patients undergoing tumor resection, 23 (75%) survived 8 months, 9 (30%) survived 16 months, and 4 (25%) survived 162 months. The group whose tumors were unable to be resected 14 (75%) survived 8 months, 9 (30%) survived 16 months, and 4 (25%) survived 162 months. The range of survival for all the patients was 1 to 275 months, with a median of 22 months. Overall 5-, 3-, and 1-year survivals were 13%, 20%, and 50%, respectively (Table 4). The median survival for the entire series was 49 months, including 12 (25%) of the patients who were alive at last follow-up. The range of survival (for all patients was 1 to 275 months, with a median of 22 months. Overall 5-, 3-, and 1-year survivals were 33%, 38%, and 77%, respectively. The group whose tumors underwent resection had significantly longer survival than those who had palliative bypass or underwent biopsy (66±13 months vs 18±5 months; P=.02). Five-, 3-, and 1-year survivals for the group that underwent tumor resection were 43%, 47%, and 90% vs the group that had palliation whose 5-, 3-, and 1-year survivals were 13%, 20%, and 50%, respectively (Figure 1). Survival analysis demonstrated that of the group undergoing tumor resection, 23 (75%) survived 20 months, 15 (50%) survived 41 months, and 8 (25%) survived 162 months. In contrast, in the group whose tumors were unable to be resected 14 (75%) survived 7 months, 9 (30%) survived 12 months, and 4 (25%) survived 41 months. The group who underwent resection had significantly longer survival than those who had palliative bypass or underwent biopsy (66±13 months vs 18±5 months; P=.02). Five-, 3-, and 1-year survivals for the group that underwent tumor resection were 43%, 47%, and 90% vs the group that had palliation whose 5-, 3-, and 1-year survivals were 13%, 20%, and 50%, respectively (Figure 1). Survival analysis demonstrated that of the group undergoing tumor resection, 23 (75%) survived 20 months, 15 (50%) survived 41 months, and 8 (25%) survived 162 months. In contrast, in the group whose tumors were unable to be resected 14 (75%) survived 7 months, 9 (30%) survived 12 months, and 4 (25%) survived 41 months. The 3 longest survivors (25%) all underwent pancreaticoduodenectomy. Two of these patients are still alive with no evidence of disease recurrence, although 1 of them had 3 positive lymph nodes at the time of resection.

MULTIVARIATE ANALYSIS

A multiple regression analysis was performed on all patients (N=49) to determine the most accurate model to predict patient survival. The best regression model resulted in 3 variables being associated with survival. These were tumor diameter, histological tumor grade, and the presence of transmural invasion. Patients with moderately to poorly differentiated tumors had decreased survival when compared with those with well-differentiated tumors (t-statistic = 2.3 [P=.03]). This survival difference is shown in Figure 2. The t-statistic for tumors that invaded through the duodenal wall into the periduodenal fat or mesentery was −3.0 (P=.004), and the t-statistic for tumor diameter was −2.6 (P=.01). The overall F statistic for the model was 4.4 (F=0.001). The r² value was 0.61.

Whether lymph nodes were involved with metastatic tumor did not influence survival (P=.25). Nor did the location of the tumor in the duodenum, the type of resection performed (pancreaticoduodenectomy vs segmental resection), and the use of adjuvant chemotherapy or radiotherapy. Table 4 summarizes the variables analyzed and their association with survival. Surgical margin was excluded from the multivariate analysis because of the small number of patients who underwent resection who had positive margins (n=3), making it statistically inappropriate to analyze the association with survival.

This study represents a retrospective review of all patients with a diagnosis of duodenal cancer who were treated at UCLA Medical Center between March 1957 and May 1998. The principal goal was to characterize the factors that were associated with survival, with the hope that this might improve the overall management of patients with this neoplasm.

One expected finding was the association between certain tumor characteristics and prognosis. Thus, large tumor diameter, a moderate to poor degree of histological differentiation, and tumor invasion into the periduodenal fat or mesentery were all associated with a shortened survival. The histological grade of duodenal tumors also was noted to be related to survival in the experience of Joesting et al., but others have found no such relationship. The explanation for such a difference is unclear, but data from other gastrointestinal malignant neoplasms generally support the relationship between the
degree of differentiation and survival. For example, patients with well-differentiated pancreatic cancers have 5-year survival that approaches 50% after resection; those with poorly differentiated tumors have 5-year survival of 10%.

Transmural invasion and large tumor size were the most significant of the predictors. In an earlier series from UCLA that included some of these same patients, Lai et al found a significant decrease in survival when there was transmural tumor invasion, with mean survivals of 42.0 months vs 10.5 months. Thus, our results extend those original observations. However, there is some disagreement in this area as well, and other studies have not found that transmural invasion influenced prognosis. Finally, as in patients with pancreatic cancer, we found an association between the size of the primary tumor and length of survival. This might have been anticipated, since larger tumors presumably have been present longer and have had more time to metastasize or invade adjacent structures. Nevertheless, in several other reviews of duodenal adenocarcinoma, such a relationship was not observed. The lack of agreement about all of these issues probably reflects the limitations inherent in retrospective reviews and, because the disease is uncommon, the small numbers of patients in most case series.

These findings do highlight the importance of early diagnosis, when the tumors are small and before they become locally invasive, to improve the chance for cure by surgical resection. Although impractical for the general population, this strongly supports routine surveillance for high-risk groups such as those with familial polyposis.

It was surprising to us that the presence of metastatic tumor in lymph nodes was not associated with decreased survival, although it is a well-known prognostic factor for other cancers of the gastrointestinal tract (eg, colon and pancreas). For example, after resection of node-positive ductal adenocarcinoma of the pancreas, the 5-year survival is about 10%. It has been reported to be as high as 40% when the lymph nodes are uninvolved. While it may be that this apparent lack of correlation is related to the limitations of this type of study already referred to, it is interesting that most of the other recent series also found no relationship between lymph node status and survival. This may be of more than academic interest since the current staging system for duodenal carcinoma assigns patients to stage III on the basis of lymph node involvement alone. Perhaps this should be reconsidered.

Analysis of the resections since 1985, compared with those done before, revealed some differences that approached, but did not attain, statistical significance. Estimated blood loss and average number of units of blood transfused decreased, perhaps indicating improvements in operative technique as well as awareness of the drawbacks of transfusion. Operative time was increased, which may reflect more aggressive tumor resections in patients who earlier would have been managed more conservatively. Postoperative morbidity was essentially unchanged, but there were no perioperative deaths in the recent group, compared with 2 in the earlier period. Finally, the length of stay in the hospital decreased in recent years.

The significance of the primary tumor location in regard to prognosis remains controversial. While 2 previous studies have shown increased survival among patients with distal tumors, others found increased survival for patients with proximal tumors. Both our current study and a recent study by Rose et al found no difference in survival based on tumor location, although there were no tumors in the first part of the duodenum in our experience.

Segmental duodenal resection has been suggested to represent a less morbid option than a pancreaticoduodenectomy for patients with tumors in the third or fourth portion of the duodenum. Our study did not reveal a survival difference between patients who underwent one or the other of those 2 operations for such tumors. This is consistent with several other reports, and seems to support segmental resection as a reasonable option for patients with cancer in this location. However, in our series only 4 of 31 patients underwent segmental resection. The previously published series also had small numbers of patients treated in this way, which could make differences in survival between more or less radical procedures hard to detect.

In summary, our 40-year experience at the UCLA Medical Center with duodenal adenocarcinoma has shown that large tumors, moderately to poorly differentiated tumors, and tumors that have invaded the surrounding fat or mesentery are associated with decreased survival. Neither metastatic involvement of lymph nodes nor the location of the tumor within the duodenum had any asso-
The paper does suffer from some of the aspects of retrospective reviews. For example, I suspect that those patients who received chemotherapy or radiotherapy as adjunct therapy probably received no uniform chemotherapy medications or a uniform method of radiotherapy. Since there were only 10 patients who received these therapies and the fact that they were not probably uniformly given makes it difficult to make a conclusion about adjunctive therapy.

In addition, I would like to ask if those patients who received adjuvant therapy were preponderantly in those groups of patients who were palliated and not resected. If this is true, certainly would make the survival statistics poorer in that group and would make the 3 groups incomparable.

I would also ask the authors to comment on lymph node involvement, ie, how many patients had lymph node involvement and did the lymph node involvement correlate with tumor grade or invasion?

Jeffrey E. Doty, MD, San Jose, Calif: I have a few questions regarding classification, staging, and treatment and one comment regarding treatment. In terms of classification I noticed in the manuscript that 10 of the patients were classified as having periampullary duodenal carcinomas, and I am wondering how your pathology department differentiates between an ampullary neoplasm and a periampullary neoplasm as I am sure you have had many more than 10 ampullary neoplasms over the last 40 years at UCLA Medical Center. Why are some in one group and others in the other group?

In terms of nodal status, as you know nodal status is a determinant of prognosis for most other GI malignacies so your data are in contradistinction to that. As well the number of lymph nodes removed by a pancreaticoduodenectomy will vary considerably between surgeons, techniques, and the pathologist examining the specimen. Did you look at the number of lymph nodes removed and see if in some way related or correlated with the nodal status? Do you have any information regarding the nodal drainage of duodenal adenocarcinomas, either with in vivo or ex vivo nodal mapping? I think this is an important issue as nodal status is a determinant in other malignancies, specifically colon cancer, for the use of adjuvant therapy.

In terms of treatment, I would question your statement in the paper that a segmental resection is “reasonable” for the management of adenocarcinoma of the third or fourth portion of the duodenum. Your splendid operative results with no mortality since 1983 would suggest to me that a radical en bloc resection is the appropriate management for a carcinoma in this area and that we should reserve segmental resection for perhaps the high-risk patient with a T1 lesion.

Finally, time permitting, would you address the role of neoadjuvant radiation chemotherapy in the patient with an advanced adenocarcinoma of the duodenum as Dr Reber has published an article regarding this in the management of locally advanced pancreatic cancer downstaging these patients to a resectable state and the role of adjuvant therapy postoperatively in those patients who have had a pancreaticoduodenectomy that has become 1 believe the standard of care at this moment for the management of cancer of the pancreas?

L. William Traverso, MD, Seattle, Wash: I rise to commend the UCLA group on 2 counts. First of all, not touched on in Dr Devesen’s lecture yesterday was the regionalization of complex surgical procedures and here in the last 15 years the UCLA group has provided support for that concept. Drs Glasgow and Mulvihill, who earlier in this program presented data on 40,000 cholecystectomy operations, several years ago presented data for California on the Whipple procedure. There were just a few institutions in California that had a very low mortality rate. It was directly related to the volume of cases that were cared for in those hospitals. I think it is significant to note that the mor-

**REFERENCES**


**DISCUSSION**

Clifford W. Deveney, MD, Portland, Ore: The authors describe a series of patients with the diagnosis of duodenal adenocarcinoma. In all, the medical records of 49 patients were reviewed. The 5-year survival for the entire series was 33%, and, for those undergoing resection, the 5-year survival was 43%. The principal predictors of survival were histological grade, presence of transmural invasion, and tumor diameter, ie, those patients with well-differentiated tumors survived longer than those with poorly differentiated ones. Something that would be logical to conclude but it is nice to have it empirically shown.

The presence of transmural invasion was also a poor prognostic sign. However, neither lymph node status nor the use of adjuvant chemotherapy or radiotherapy affected survival in this series. The paper is a well-done retrospective review of this disease, and I would agree with the authors that we can conclude principally from these studies that we should be fairly aggressive in the surgical treatment of those smaller tumors that have not extensively invaded surrounding structures, and we can expect a 5-year survival in the neighborhood of 50% in those types of patients.
tality rate in the last 15 years at UCLA with pancreaticoduodenectomy is lower than that published for cholecystectomy.

Second, UCLA is the home of the Isacoff regimen that has been shown, as alluded to by Dr Doty, to be a significant intervention in increasing survival. This regimen has also been observed to decrease the size of pancreatic cancer performed in a neoadjuvant setting. This Isacoff regimen is going on to be tested more nationally in a multicenter clinical trial so it is commendable to note that this came out of UCLA. My one question to the UCLA group is, if you have a duodenal carcinoma, would you use the Isacoff regimen in an adjuvant setting? What is your current treatment for these nonpancreatic periampullary tumors?

James E. Goodnight, Jr, MD, PhD, Sacramento, Calif:
At the risk of redundancy, if you have a 2.5-cm carcinoma on the greater curve, outside curve of the duodenum, would you resect that with a wedge resection? Would you reiterate what you consider a small tumor?

Dr Reber: Dr Deveney, chemotherapy and radiotherapy was not uniformly given to the patients in this group. Generally speaking, you are correct in your assumption that the adjuvant therapy was given to those patients who did not undergo resection. Thus, that may very well be the reason those patients did not seem to respond well to the adjuvant treatment, i.e., they had more advanced disease and the disease was still present.

About 43% of patients had lymph node involvement. We all recognize that there is significant variability in terms of how many nodes are removed by the individual surgeons whose operative approach may be a little bit different. There is no question that the number of nodes that individual pathologists digs out of the specimen varies greatly as well. Even the same surgeon doing a Whipple resection the same way every time will produce specimens with 5 or 6 nodes with one pathologist, and up to 20 or 25 with another. Too, may be part of the explanation for why in this retrospective analysis we really did not find any correlation with lymph node involvement in terms of prognosis.

Dr Doty wondered about whether a segmental resection really is the operation to do in patients who have lesions in the fourth portion of the duodenum. I do understand his concern about whether that is really an adequate operation. Nevertheless, it is hard to look past the fact that in virtually all the series that have been presented where segmental resections have been done for these distal lesions, the survival statistics are really quite good and no different than in patients who undergo the more radical resections.

There were many questions that had to do with the issue of adjuvant and neoadjuvant therapy, and as Dr Traverso mentioned, the so-called Isacoff regimen. I will say a couple of words about that. The Isacoff regimen consists of continuous infusion of fluorouracil, mitomycin C, leucovorin calcium, and oral dipyridamol. These drugs are given in combination usually over a period of about 6 months. We do not use neoadjuvant therapy with this or any other regimen for either pancreatic or duodenal adenocarcinomas. In part, this is because the overall response rate is only about 35%. The vast majority of patients with pancreatic cancer receive these drugs in the adjuvant setting. Those with duodenal cancers often do as well, but there is no standardized approach.

Dr Goodnight asked the question about how we would manage a small adenocarcinoma of the duodenum on the lateral wall. In a patient with a lesion in the first, second, or third portion of the duodenum we would do a Whipple resection of its pylorus-preserving modification. If the patient had a small lesion in the fourth portion of the duodenum, that individual would be a reasonable candidate for a segmental resection.

ARCHIVES OF INTERNAL MEDICINE

Hyperhomocyst(e)inemia and the Increased Risk of Venous Thromboembolism: More Evidence From a Case-Control Study

Loralie J. Langman, PhD; Joel G. Ray, MD, FRCP; Jovan Evrovski, PhD; Erik Yeo, MD, FRCP; David E. C. Cole, MD, FRCP

Background: Elevation of plasma homocyst(e)ine level is an independent risk factor for arterial and venous thrombosis. We studied the degree to which hyperhomocyst(e)inemia contributes to the development of venous thromboembolism, using a retrospective case-control study design.

Methods: Cases were individuals with objectively confirmed venous thromboembolism and no history of atherosclerosis seen at the Toronto Hospital Thrombosis Clinic, Toronto, Ontario, between January 1, 1996, and July 31, 1998. Three controls were matched for every case according to sex and age within 5 years and were derived from a large community cohort. All subjects underwent assessment for fasting plasma homocyst(e)ine levels. Hyperhomocyst(e)inemia was defined as fasting total homocyst(e)ine concentration above the 95th percentile control value.

Results: Seventy cases and 210 matched controls were included. Men and women were equally represented, and most were younger than 60 years. Among cases with venous thromboembolism, the mean (± SD) plasma homocyst(e)ine level was significantly higher than in controls (13.0 ± 6.9 µmol/L vs 9.0 ± 4.8 µmol/L, respectively; P < .001). Sixteen (23%) of 70 cases had hyperhomocyst(e)inemia compared with 10 (5%) of 210 controls (odds ratio, 5.9; 95% confidence interval [CI], 2.5-13.8). Among subjects aged 60 years or younger, the odds ratio was 4.9 (95% CI, 1.4-16.4), while for those aged 60 years or older, it was 7.3 (95% CI, 2.2-24.0). Even with the exclusion of cases showing abnormal renal function or low serum vitamin B12 or folate levels, the odds ratio remained significantly elevated at 3.3 (95% CI, 1.1-10.0).

Conclusions: We found that fasting hyperhomocyst(e)inemia is a significant risk factor for venous thromboembolic disease in patients at a thrombosis clinic. Given the magnitude of effect and consistency across these studies, it is likely that homocyst(e)ine plays a causative role in the development of venous thrombosis, and it should be considered in the workup for venous thromboembolism.

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