Metastases to the Pancreas and Their Surgical Exirpation

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Background: The pancreas is an unusual but occasionally favored site for metastases, notably from carcinomas of the kidney and lung. The pancreas may be the only identified locus of spread, and therefore may provide an opportunity for significant palliation or even cure using pancreatectomy.

Objective: To report the treatment and outcome of patients presenting with metastases to the pancreas.

Design: Five-year survey.

Setting: Tertiary referral center.

Patients: Ten patients with apparently isolated metastases to the pancreas were identified from January 1, 1991, to December 31, 1995. All patients were followed up until death or to September 1997.

Results: The patients had been treated previously for carcinoma of the lung (n=4), renal cell carcinoma (n=2), sarcoma (n=2), breast carcinoma (n=1), and endometrial carcinoma (n=1). The interval between primary treatment and presentation of the metastases averaged 70 months (14-24 months for lung cancer, 10 and 22 years for renal cell carcinoma, 4 and 6 years for sarcoma, 8 years for breast cancer, and 36 months for endometrial carcinoma). Metastases were initially misdiagnosed as primary pancreatic cancers in 7 patients. In 4 patients (those with renal cell cancer and sarcomas), the tumor was completely resected using total pancreatectomy (n=3) or Whipple resection (n=1). Survival after diagnosis averaged 22 months. Two of the 4 patients undergoing pancreatic resection remain alive and well 20 and 25 months after pancreatectomy.

Conclusions: The pancreas may be the presenting and perhaps sole locus for metastasis, typically years after treatment for certain extrapancreatic malignant neoplasms. Recognition and surgical treatment can provide worthwhile palliation and long-term survival.

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Metastasis of other cancers to the pancreas is much more frequent than commonly appreciated. In fact, metastatic cancer is found much more frequently from tumors other than primary pancreatic cancer in autopsy series. Although most of these are incidental findings in patients with widely disseminated malignant disease,1 isolated metastases have been reported.2 If a metastasis in the pancreas becomes symptomatic, it is likely to be misdiagnosed as a primary tumor, especially if it appears to be a solitary lesion. We have had the opportunity to treat a series of patients with cancer metastatic to the pancreas. We have made the common errors of diagnosis but also found that aggressive treatment with resection when possible can provide useful palliation and possible cure.

See Invited Commentary at end of article

From the Departments of Surgery, Massachusetts General Hospital and Harvard Medical School, Boston, Mass.

RESULTS

Six male and 4 female patients (Table 1) with a median age of 57 years (range, 42-71 years) had been treated previously for carcinoma of the lung (n=4), renal cell carcinoma (n=2), sarcoma (n=2), breast carcinoma (n=1), and endometrial carcinoma (n=1). The presenting clinical symptoms were jaundice (n=4), acute pancreatitis (n=3), pain (n=3), weight loss (n=3), duodenal obstruction (n=2), and upper gastrointestinal tract bleeding (n=1). The interval between primary treatment and presentation of the metastases to the pancreas averaged 70 months (14-24 months for lung cancer, 10 and 22 years for renal cell carcinoma, 4 and 6 years for sarcoma, 8 years for breast cancer, and 3 years for endometrial carcinoma).

This article is also available on our Web site: www.ama-assn.org/surgery.
PATIENTS AND METHODS

Ten patients with apparently isolated metastases to the pancreas were identified from January 1, 1991, to December 31, 1995, in our surgical practice at the Massachusetts General Hospital, Boston. All patients were followed up until death or September 1997. Clinical presentation, treatment, and survival were the main outcome measures.

An abdominal computed tomographic (CT) scan (Figure 1) allowed or confirmed the diagnosis of a tumor of the pancreas in 9 patients; in the other patient, the initial abdominal CT scan demonstrated a dilation of the bile duct and pancreatic duct (double duct sign) without a visible mass in the head of the pancreas. The tumors were initially misdiagnosed as primary pancreatic cancers in 7 of 10 patients. Results of fine needle aspiration of the pancreas gave a definitive diagnosis in only 3 of 6 cases. Endoscopic retrograde cholangiopancreatography was performed in 6 patients and showed dilated bile and pancreatic ducts in 3 patients with solitary masses of the pancreatic head and midpancreatic duct obstructions in 2 patients with multiple metastases of the pancreas. One patient with multiple metastases from a renal cell carcinoma had normal findings on endoscopic retrograde cholangiopancreatography.

In 4 patients (those with renal cell cancer and sarcomas), the tumor was resected with intention to cure using total pancreatectomy (n=3) or Whipple resection (n=1) (Table 1). Figure 2 demonstrates the operative specimen from a patient with primary renal cell cancer and isolated metastases to the pancreas (patient 9; Table 1). The other 6 patients had only palliative treatment, including surgical bypasses to relieve obstructive jaundice and duodenal obstruction (n=3) or endoscopic stenting of the bile duct (n=2). In the latter 2 patients, the tumor was staged as unresectable using preoperative CT scan and/or angiography.

Survival after diagnosis averaged 22 months (median, 19 months; range, 12-54 months). Two patients lived 34 and 54 months. Two of the 4 undergoing pancreatic resection remain alive and well after 20 and 25 months.

In large autopsy surveys, the prevalence of metastasis to the pancreas is as high as 11%; lung, colon, and breast cancer being the most common tumors of origin. Many of these patients have widespread disease, and isolated symptomatic metastases to the pancreas are rare. In a clinical series of patients with pancreatic tumors, 4.5% of cases were found to be metastases, and that figure increased to 42% among patients with previously diagnosed primary cancers and a solitary mass of the pancreas. Although there may be suspicion of metastasis, the differentiation of a primary from a secondary neoplasm may require tissue sampling for histological examination. Even so, results of percutaneous biopsies failed to establish the correct diagnosis in 3 of 6 attempts in our series. A definitive diagnosis was only possible at open operation in most of our cases.

The symptoms from neoplasms of the pancreas commonly include pain, weight loss, and obstructive jaundice. Upper gastrointestinal tract bleeding and acute pancreatitis are less common but well-recognized in patients with primary pancreatic cancer. Acute pancreatitis was the presenting feature in 3 of our 10 patients. Its pathogenesis is likely to be related to pancreatic duct obstruction by the tumor inasmuch as 2 of those 3 patients had results of pancreatograms demonstrating a block in the body of the gland. Pancreatitis has previously been reported following metastatic lung carcinoma and melanoma.

The preoperative diagnosis of metastasis to the pancreas begins with suspicion based on the history of a relevant cancer. Imaging studies such as dynamic contrast-enhanced CT scans and magnetic resonance imaging (MRI) may support that suspicion, especially if multiple tumors are noted. Highly vascular tumors, as indicated by contrast-enhanced CT, MRI, or angiography, are more likely to be metastases than primary pancreatic cancers, which tend to be relatively hypovascular. These findings are particularly applicable for renal cell carcinoma, as shown in Figure 3, but must still be distinguished from primary neuroendocrine tumors, which are also hypervascular. Metastasis may also be more likely when there is a large tumor of the pancreatic head without a dilated bile duct and when the retropancreatic fat is not obliterated in a patient with a large pancreatic mass.

Table 1. Site of Primary Tumor and Clinical Presentation of Patients With Metastases to the Pancreas

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Diagnosis</th>
<th>Interval Between Primary Treatment and Metastasis</th>
<th>Presenting Symptoms</th>
<th>Location and Size of Metastases at Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lung cancer</td>
<td>14 mo</td>
<td>Gastrointestinal bleeding</td>
<td>Head of the pancreas, solitary, 3 cm</td>
</tr>
<tr>
<td>2</td>
<td>Lung cancer</td>
<td>16 mo</td>
<td>Jaundice</td>
<td>Head of the pancreas, solitary, 6 cm</td>
</tr>
<tr>
<td>3</td>
<td>Lung cancer</td>
<td>18 mo</td>
<td>Jaundice</td>
<td>Head of the pancreas, solitary, 3 cm</td>
</tr>
<tr>
<td>4</td>
<td>Lung cancer</td>
<td>2 y</td>
<td>Jaundice</td>
<td>Uncinate process, solitary, 2 cm</td>
</tr>
<tr>
<td>5</td>
<td>Endometrial cancer</td>
<td>3 y</td>
<td>Duodenal obstruction</td>
<td>Uncinate process, solitary, 4 cm</td>
</tr>
<tr>
<td>6</td>
<td>Breast cancer</td>
<td>8 y</td>
<td>Jaundice, weight loss</td>
<td>Head of the pancreas, solitary</td>
</tr>
<tr>
<td>7</td>
<td>Chondrosarcoma of the forearm</td>
<td>6 y</td>
<td>Pancreatitis</td>
<td>Head, body, and tail of pancreas; multiple: 0.2-6.0 cm</td>
</tr>
<tr>
<td>8</td>
<td>Malignant fibrous histiocytoma</td>
<td>4 y</td>
<td>Duodenal obstruction, weight loss</td>
<td>Head of the pancreas, solitary, 9×5 cm</td>
</tr>
<tr>
<td>9</td>
<td>Renal cell cancer</td>
<td>10 y</td>
<td>Pancreatitis, weight loss</td>
<td>Head, body, and tail of pancreas; multiple: 0.4-3.5 cm</td>
</tr>
<tr>
<td>10</td>
<td>Renal cell cancer</td>
<td>22 y</td>
<td>Pancreatitis</td>
<td>Head, body, and tail of pancreas; multiple: 0.5-3 cm</td>
</tr>
</tbody>
</table>
Metastases to the pancreas from a number of different tumors have been described in single-case reports or small clinical series. Roland and van Heerden found that colon (n=6) and lung (n=5) were the most common sites of origin of apparently isolated metastasis to the pancreas in 27 patients treated at the Mayo Clinic, Rochester, Minn. In their experience, the mean survival was short (8.7 months, with 26 months the longest survival). In contrast, we found that the lung was the site of the primary cancer in 4 of 10 patients, but none had metastasis of colorectal cancer. All 4 patients with lung cancer metastasis survived longer than 12 months after surgical or endoscopic palliative procedures and with chemotherapy for their systemic disease, but none of the tumors was resectable.

Indications for pancreatic resections for metastasis have not been defined. Some writers consider pancreatectomy as long as results of preoperative radiological studies demonstrate no evidence of metastases to organs other than the pancreas. Curative resection, surgical or endoscopic palliation, or chemotherapy alone is then chosen according to the particular requirements of the clinical presentation and the expected outcome. As illustrated in our series, resection is most likely to be warranted in patients presenting after a long disease-free interval following the primary operation, suggesting a biological pattern of slow growth. The duration of our patients’ survival may be as much due to the characteristics of their tumors as to our intervention.

Jaundice in patients with breast cancer is most likely to be the result of multiple metastases replacing the liver parenchyma, and the onset of jaundice is an ominous sign associated with a mean survival of only 1 month. However, in a small subset of patients, jaundice is caused by extrahepatic bile duct obstruction by metastases to lymph nodes or to the pancreas. Relief of the extrahepatic bile duct obstruction using surgical bypass or biliary stent may produce extended survival exceeding 1 year. One of our patients who presented with obstructive jaundice 8 years after mastectomy for a lobular breast cancer survived 54 months after a hepaticojejunostomy and gastrojejunostomy and appropriate chemotherapy. Pancreatic resection may be possible in exceptional cases and provide even longer survival.

Metastases are solitary in fewer than 10% of patients with metastatic renal cell cancer. Resection of isolated metastases may contribute to prolonged survival in a small subgroup of these patients. More than 50 cases of pancreatic resections for metastatic renal cell cancer have been reported, and it would appear that these are the most frequent surgically treated metastases to the pancreas. As in our experience, these patients characteristically present with a long disease-free interval (>11 years on average) between primary tumor resection and recognition of metastasis to the pancreas. More than 80% of the patients undergoing pancreatectomy survive longer than 12 months, but an accurate estimate of the average survival is difficult to assess, since the majority of cases are reported within 2 years of pancreatic resection. One case of long-term survival has been reported, and 5-year survival of 31% has been predicted for patients undergoing resection of pancreatic metastasis due to renal cell carcinoma. This survival is even better than that of patients with resected primary pancreatic adenocarcinoma, for whom 5-year survival is between 15% and 20%.

Sarcomas frequently metastasize to the lungs, and pulmonary resection achieves long-term survival in ap-

Table 2. Procedures and Survival in Patients With Metastasis to the Pancreas

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Procedure</th>
<th>Cause of Unresectability</th>
<th>Survival After Resection or Palliation, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Exploratory laparotomy</td>
<td>Preoperatively undetected liver metastases</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>Laparoscopy, endoscopic retrograde cholangiopancreatography, and stent</td>
<td>Angiographic vascular infiltration by tumor</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>Endoscopic retrograde cholangiopancreatography and stent</td>
<td>Locally advanced disease</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>Biliary and gastric bypass</td>
<td>Invasion of mesenteric vein by tumor</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>Biliary and gastric bypass</td>
<td>Locally unresectable</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>Biliary and gastric bypass</td>
<td>Omental carcinomatosis</td>
<td>54</td>
</tr>
<tr>
<td>7</td>
<td>Total pancreatectomy</td>
<td>...</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>Whipple resection</td>
<td>...</td>
<td>25†</td>
</tr>
<tr>
<td>9</td>
<td>Total pancreatectomy</td>
<td>...</td>
<td>20†</td>
</tr>
<tr>
<td>10</td>
<td>Total pancreatectomy</td>
<td>...</td>
<td>20†</td>
</tr>
</tbody>
</table>

* Ellipses indicate not applicable.
† Indicates patient still alive.
proximately 30% of patients. Synchronous metastases to other organs such as the heart, thyroid, stomach, or pancreas are often reported at the time of diagnosis of lung metastases. An aggressive surgical approach to isolated metastases is recommended, and the reported cases with sarcoma metastases to the pancreas were treated according to these recommendations. Detectable widespread metastatic disease developed soon after pancreatectomy in our patient with a chondrosarcoma, who underwent excision of mediastinal metastases 2 years before the detection of a pancreatic metastasis. The patient died 6 months postoperatively. In contrast, the solitary pancreatic metastasis was the first manifestation of spread in our patient with the malignant fibrous histiocytoma, and the patient is disease-free and well 25 months after pancreatectomy.


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REFERENCES


Kirby Bland, MD, Providence, RI: Dr Z’graggen and his associates raise the interesting possibility that the pancreas may be the presenting and perhaps the sole locus for metastatic extrapancreatic malignancies. This hypothesis inspired the authors to derive a management algorithm for aggressive surgical management that may provide significant palliation and long-term survival in this patient population. As in other solid neoplasms, the expected variations in survival may be directly attributable to (1) disease-free interval and (2) tumor histology (especially in renal cell carcinoma, sarcoma, and breast cancer). Other tumor variables that clearly influence disease-free interval and overall survival include (1) grade, (2) American Joint Committee on Cancer stage, (3) cell-proliferative indices (flow cytometry), and (4) oncogene expression. The relative weight of these variables is clearly difficult to ascertain for this small series. So I have a few questions and comments.

Please explain how you determine the best candidates for resection. To what extent should the workup be pursued, and what biological marker (if any) would you consider; which invasive diagnostic studies (MRI, endoscopic ultrasonography) are appropriate?

As we are aware, many patients are referred after CT-guided biopsy reveals pancreatic neoplasms. If you have control of a patient early in management, do you defer biopsy until the intraoperative evaluation?

My next question concerns the role of laparoscopic staging in determining resectability. If patients do not present with symptoms requiring palliative biliary or gastrointestinal bypass, do you recommend laparoscopic staging to determine resectability? Or would you embark on an open procedure with the option of performing resection if the operative findings call for it?

You state that the existing literature provides no clear indications for resections with this presentation. However, your standard procedure is to complete formal pancreatectomy (Whipple or total) based on the anatomical presentation of the metastasis, the probability of a curative en bloc resection, and the projected disease-free interval. Thus, my last questions: Would a projected short disease-free interval in the more favorable histologies (renal cell, sarcoma) dissuade you from formal resection, even if other criteria would lead you to favor resectability? If other anatomical or radiological criteria suggest no extrapancreatic disease, what length of projected disease-free interval would trigger your decision not to perform a resection?

Charles Shoemaker, Jr, MD, Newport, RI: I would just like to reinforce Dr Bland’s question about fine-needle aspiration (FNA). The MGH experience and the paper yesterday indicated that FNA is associated with metastatic or intraperitoneal spread, and I wonder if that is still the protocol for this type of tumor.

Harold J. Wanebo, MD, Providence: A question about the patients that have a past history of colorectal cancer or breast cancer. If one uses some of these imaging techniques, such as the Oncoscint, you may get localization right in the pancreas. Would you consider this as a resectable tumor?

Dr Z’graggen: I would like to emphasize again that this is a selected, carefully evaluated subset of patients with apparently isolated metastases to the pancreas. These patients were referred to the surgical practice of Dr Warshaw for possible surgical treatment.

What patient with a metastasis to the pancreas is a good candidate for pancreatic resection? We mentioned in the paper that favorable prognostic factors are a long interval between the treatment of the primary tumor and the appearance of the metastasis to the pancreas, indicating a favorable tumor biology and a slow growth pattern. However, we did not investigate their individual growth characteristics, either from biopsies preoperatively or in the resected specimens, to relate those to outcome. We also take into account the primary tumor and the treatment options for this tumor. In renal cell carcinomas and sarcomas, resection is the only treatment that provides a chance for cure, and these patients are therefore candidates for surgery. With other cancers, such as breast carcinoma, chemotheraphy alone could be an effective option. However, patients with peritoneal metastases causing obstructive jaundice must be decompressed either by stenting or by surgical bypass.

What is the significance of MRI and endoscopic ultrasound examinations in patients with metastasis to the pancreas? An MRI may allow the diagnosis of a hypervascular tumor, eg, a renal cell cancer metastasis, but neither MRI nor endoscopic ultrasound will be able to distinguish with certainty between a primary or secondary pancreatic tumor. A tissue biopsy or FNA still needed for diagnosis.

The best examination to determine resectability of any pancreatic tumor is, in our experience, dynamic contrast-enhanced helical CT scan. Endoscopic ultrasound may be a valuable adjunct to determine resectability in specific cases, but it is very dependent on the experience of the examiner. Laparoscopic examination will be able to distinguish with certainty between a primary or secondary pancreatic tumor. A tissue biopsy or FNA still needed for diagnosis.

Are FNAs indicated in patients with metastases to the pancreas? Because of a potentially increased risk of peritoneal tumor dissemination associated with the procedure, we generally do not perform FNA for the evaluation of primary pancreatic adenocarcinoma, but we have no evidence to indicate similar concern with metastases to the pancreas. In these unusual circumstances, confirmation of the diagnosis is particularly important, especially for tumors that could be treated by chemotherapy.

Although our series does not include patients with colorectal metastasis to the pancreas, most of the reported cases had extensive metastatic disease in the abdominal cavity and/or the lungs and were therefore not candidates for resection.

Finally, Dr Tsao mentioned 2 surgically treated long-term surviving patients with renal cell carcinoma metastatic to pancreas. Among the more than 60 cases of renal cell carcinoma metastatic to pancreas described in the literature, over 50 cases were resected with curative intent, but only a minority (less than 10%) were reported to be long-term survivors. Nonetheless, the effort seems worthwhile.