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Metastatic Tumors in the Pancreas in the Modern Era

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Abstract

BACKGROUND—Tumors metastasizing to the pancreas are rare, and published series are limited by few patients treated for extended periods of time. Renal cell cancer (RCC) is the most common primary tumor metastasizing to the pancreas. Our aim was to describe the clinicopathologic characteristics and patient outcomes in a modern series of patients who underwent metastasectomy, with an emphasis on RCC.

STUDY DESIGN—Retrospective review of all pancreatic resections between January 1993 and October 2009.

RESULTS—We identified 40 patients with a median age of 62 years; 55% were female. Patients most commonly presented with abdominal pain (47.5%). Operations performed included 10 pancreaticoduodenectomies, 1 middle, 23 distal, 3 total pancreatectomies, and 3 enucleations. Primary cancers were RCC (n = 20), ovarian (n = 6), sarcoma (n = 3), colon (n = 3), melanoma (n = 2), and others (n = 6). Median survival for all patients after metastasectomy was 4.4 years. Median survival after metastasectomy for RCC was 8.7 years, and the 5-year actuarial survival was 61%. For RCCs, pancreas was the first site of an extrarenal recurrence in 85% and was synchronous with the primary in 5% of patients. There was no survival difference if the time interval to metastasis was shorter than the median (8.7 years), if tumor nodules were multiple or bigger than the median (3 cm), or if the pancreas was not the first site of metastases.

CONCLUSIONS—An aggressive approach to lesions metastatic to the pancreas is often warranted if the patient can be rendered free of disease. Although patients with RCC can experience long-term survival after metastasectomy, survival is less favorable for other primary tumors.

Most patients with metastases to the pancreas have widespread metastatic disease and are not candidates for resection. Not surprisingly, pancreatic metastasectomies account for <4%

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of all pancreatic resections.^{1,2} Because of the rarity of metastases to the pancreas, there have been no prospective randomized trials to address the role of surgical resection. Therefore, the role of pancreatic resection for metastases is still unclear. However, as the morbidity and mortality of pancreatic surgery improves, the enthusiasm for surgical resection of pancreatic metastases has increased.³ The most common cancers reported to metastasize to the pancreas include renal cell cancer, colon cancer, melanoma, sarcoma, breast, and lung cancer.^{4,5}

Resection of metastases has demonstrated a survival benefit for some cancers. A growing body of literature supports the potential for long-term survival in select patients undergoing metastatectomies from a variety of different primary tumors, such as breast, renal cell cancer, and sarcoma. In gastrointestinal cancers, the strongest survival benefit has been observed in patients with colorectal cancer and hepatic metastases.^{6,7} As the data for metastatectomies become more robust, the role for pancreatic resections for metastatic disease is being examined more closely as part of the multidisciplinary care plan of patients.

The aim of our study was to report our experience with 40 patients who underwent pancreatic resections for metastases during the past 17 years. Our second aim was to define prognostic factors for survival in patients undergoing pancreatic resections for renal cell cancer metastases.

METHODS

Study design

A retrospectively created database (January 1, 1993 to January 1, 2001) and a prospectively maintained database (January 1, 2001 to October 15, 2009) were reviewed to identify patients who underwent surgical resection of cancers metastatic to the pancreas. All resections were performed with curative intent. Primary tumors that involved the pancreas through direct extension were excluded from this study. Patients who had other metastatic sites synchronous with the pancreatic metastasis were included only if they were rendered as having no evidence of disease by the operation. Patients with ovarian cancer underwent a distal pancreatectomy as part of cytoreductive surgery.

Clinical data included sex, age, presenting symptoms, operative procedures, and disease-specific survival. Pathological data included tumor size, histological type, degree of differentiation, presence of perineural, lymphatic, perivascular invasion, and surgical margin status. Operative mortality was defined as death within 30 days of operation. Overall survival was calculated from the date of metastasectomy to the time of death or last follow-up. With regard to the incidence of postoperative pancreatic fistula, we defined pancreatic fistula according to the International Study Group on Pancreatic Fistula criteria.⁸ This study was approved by the IRB of the Massachusetts General Hospital.

Statistical analysis

Statistical analysis of the data was performed using SPSS 11.0 for Windows (SPSS, Inc.). Continuous variables were dichotomized at their median values for the purpose of statistical analysis.

Comparisons for continuous variables with normal distributions were conducted with *t*-test and for continuous variables without normal distributions by Mann-Whitney test. Categorical variables were analyzed using the chi-square test. Survival curves were constructed with the Kaplan-Meier method. Univariate comparisons were performed with the log-rank method. Level of statistical significance was set at $p = 0.05$.

RESULTS

During the past 15 years, 2,224 patients have undergone pancreatic resections for a variety of pathologies. Of the 2,224 patients, 40 (1.8%) underwent pancreatic resections for metastases from extrapancreatic primaries. Clinicopathologic factors are listed in Table 1. Median age was 62 years and 55% were female. Abdominal pain was the most frequent presentation, although in 32.5% of patients the metastases were incidentally discovered. Renal cell carcinoma (RCC) was the most frequent tumor metastasizing to the pancreas (50%).

The majority of patients underwent a distal pancreatectomy (57.5%). Multiorgan resections, consisting of distal pancreatectomies with additional organs other than the spleen resected, were performed in 11 patients (27.5%). Additional organs resected included omentum (n = 4), colon (n = 4), liver (n = 3), kidney (n = 2), peritoneum (n = 2), uterus/fallopian tubes/ovaries (n = 3), and diaphragm (n = 1). Ovarian cancer was the most frequent cancer for which extended operations were performed (n = 6). Of these patients, 3 had synchronous metastases to the pancreas and 3 had metachronous metastases to the pancreas. Extended resections were also performed for RCC (n = 2), esophageal adenocarcinoma (n = 1), colonic adenocarcinoma (n = 1), and gastric leiomyosarcoma (n = 1). Limited resections (3 enucleations and 1 middle pan-createctomy) were performed for RCC metastases.

The intent of surgical resection was to render patients as having no evidence of disease, however, surgical margins were microscopically positive in 5 of 40 of patients. Lymph nodes were positive in 7 of 20 patients evaluated. Positive lymph nodes were identified in patients with RCC (n = 3), ocular melanoma (n = 1), fallopian tube carcinoma (n = 1), colon adenocarcinoma (n = 1), and testicular germ cell cancer (n = 1).

Overall mortality was 2.5% (n = 1). The only postoperative death was a woman with advanced ovarian cancer. Postoperatively, complications developed in 37.5% (15 of 40) of patients (Table 1). The rate of pancreatic fistula was 27.5%. Median length of hospital stay was 8 days (range 3 to 82 days). Median and mean follow-up for the entire cohort were 20.5 and 35.8 months, respectively (range 0 to 186.3 months). Median actuarial survival was 4.4 years and the 5-year actuarial survival was 42%. Patients with renal cell carcinoma metastases had more favorable outcomes compared with patients with other cancers (Table 2, Fig. 1). Patients with ovarian cancer, who constituted the majority of the extended resections group, had a short overall survival (median survival of 1.3 years) despite debulking of their disease.

RCC

RCC was the most common tumor to present with resectable metastases to the pancreas (n = 20). The majority of patients were male (65%) with a median age of 68.5 years (range 44 to 84 years) (Table 3). The location of the primary tumor did not predict the site of the metastasis in the pancreas (right RCCs metastasized 4 of 11 to the head and neck, 4 of 11 to the body and tail, and 3 of 11 to multiple sites throughout the pancreas; p = 0.39).

The majority of patients experienced metachronous disease (19 of 20), with pancreatic metastasis as the first site of extrarenal recurrence in the majority of patients (16 of 20). Two patients experienced recurrent RCCs on the contralateral kidney before metastasizing to the pancreas. Median time between resection of the primary renal cell cancer and the pancreatic metastasectomy was 8.7 years (range 0 to 22 years). Four patients underwent treatment of a different metastatic locus before the pancreatic metastasis (ie, brain, lung, thyroid, skin).

Metastatic nodules were solitary in 75% (15 of 20) of patients. Two metastases were identified in 1 patient and >2 metastases were identified in 4 patients. Multiple nodules necessitated a total pancreatectomy in 2 patients and a completion total pancreatectomy in 1 patient. Three patients underwent enucleation of their metastasis, and 1 patient underwent a middle pancreatectomy. The median size of the metastatic nodules was 3 cm (range 0.8 to 12 cm). Twelve patients had lymph nodes evaluated, of which 3 had positive lymph nodes. The median number of evaluated lymph nodes was 7.5. In 1 patient the disease was limited to the peripancreatic nodes and the adjacent pancreatic parenchyma was not infiltrated.

Patients with RCC metastases had a median and mean follow-up of 36.8 and 38.1 months, respectively (range 0.5 to 143 months). Their median survival from the time of metastasectomy was 8.7 years (range 1.3 to 12 years) and 5-year actuarial survival was 61%. The single patient who had a pancreatic metastasis synchronous with his primary tumor survived only 15 months. The 3 patients who underwent enucleation of the metastases and the patient who underwent a middle pancreatectomy had no evidence of local recurrence after 3.5, 12.6, 47.3, and 72.8 months, respectively.

On univariate analysis, the number of metastatic nodules (solitary versus multiple, $p = 0.87$), the size of metastasis (greater or smaller than the median of 3 cm, $p = 0.78$), the location of the metastasis ($p = 0.72$), or an R1 resection ($p = 0.62$) had no prognostic significance for overall survival. Hemoglobin values below the lower level of the reference range also did not predict worse outcomes ($p = 0.99$).

DISCUSSION

Metastatic tumors to the pancreas are rare. No prospective randomized or case-controlled studies have been performed to evaluate the role of surgical resection. Yet many of the existing retrospective studies are limited because of the small number of patients who were treated during prolonged periods of time. This is one of the largest single-institution reports of resections for metastases to the pancreas and provides insights into the role of surgical resection as part of the multidisciplinary management of these patients. Similar to other series,^{3,4,9} a variety of tumors presented with pancreatic metastases. Median overall survival varied from 0.6 years to 15.5 years based on the primary malignancy. Patients with RCC primaries had the most favorable survival, although patients with ovarian cancer, colon cancer, and sarcoma had the poorest survival.

The majority of patients underwent an isolated pancreatic resection. However, multiorgan resections were also performed in an effort to render patients as having no evidence of disease. The most common indication for a multiorgan resection was a primary or secondary cytoreductive operation for ovarian cancer. Despite aggressive surgical resections, overall survival of ovarian cancer patients was poor in our series. Median survival of ovarian cancer patients undergoing pancreatic resections in our series was only 1.3 years. This is similar to the median survival of 1.8 and 1.7 years after primary and secondary cytoreduction of upper abdominal disease described by Magtibay and colleagues.¹⁰ Although extensive upper abdominal disease appears to be a poor prognostic factor, there are some patients who will survive longer than 5 years after a cytoreductive operation.¹¹ Therefore, pancreatic involvement should not preclude an aggressive surgical strategy in patients with ovarian cancer.

In our series, 50% of patients underwent a pancreatic resection for RCC metastases, which is similar to the 61.7% of patients with RCC in the review by Reddy and colleagues.⁵ For both cohorts, median survival (8.7 years) and 5-year survival (61% versus 66%) were similar. Prognostic factors for metastatic RCC identified in other studies included time from

diagnosis to adjuvant treatment >12 months, hemoglobin values higher than the lower normal limit, and <2 metastatic sites.^{12,13} We were not able to validate these factors with our cohort of patients. Neither the disease-free interval, number of metastases, nor hemoglobin were substantial prognostic factors for survival in patients who underwent pancreatic resection for RCC metastases.

Renal metastases synchronous with the primary renal cell cancer occurred in only 1 patient in our study and was associated with poor outcomes, similar to findings of Reddy and colleagues.⁵ Median time from the primary resection to the metastasectomy was 8.7 years in our patients, but even metastasis during the first 2 years after the resection of the primary did not necessarily preclude long-term survival.⁵ Similarly, the size of the metastatic nodules did not impact survival. Lymph node involvement is of uncertain prognostic significance; however, it occurs only rarely with RCC.⁵ Multifocality or larger metastatic nodules can lead to more extensive operations, but did not preclude long-term survival, as also documented by Sellner and colleagues.¹⁴ Additionally, patients in our series who had already undergone treatment for a different metastatic locus before their pancreatic resection were able to experience long-term survival.

The role of local resections, including segmental resections and enucleations, for the treatment of RCC metastases to the pancreas is uncertain. Although Bassi and colleagues reported a higher morbidity rate and a local recurrence rate of 50% after local resections,¹⁵ our series, like that of Zerbi and colleagues,¹⁶ had no local failures with limited resections. Performing a limited resection with adequate margins and ensuring the absence of other tumor nodules in the pancreatic parenchyma appears to be comparable with a formal resection for renal cell cancer metastases to the pancreas.

Potential weaknesses of this study are related to its retrospective nature. Additionally, the relatively limited number of patients with RCC metastases increases the likelihood of a type II statistical error. Prospective studies would better address the role of surgical therapy in pancreatic metastasectomy. However, because of the rarity of these lesions, such a trial can only be performed in a multi-institutional setting and possibly only for RCC metastases because of their high relative incidence compared with other cancers.

CONCLUSIONS

Pancreatic resections for metastases should be considered as part of the multidisciplinary management of patients if they can be rendered free of disease. This highly select group of patients can achieve long overall survival, especially in the setting of a primary RCC.

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Figure 1.

Patients who underwent pancreatic resection for metastases from renal cell cancer experience a longer survival compared with other extrapancreatic malignancies. CRC, colorectal cancer; RCC, renal cell cancer.

Table 1**Clinicopathologic Characteristics of Patients**

Age, y, median	62
Female sex, n (%)	22 (55)
Asymptomatic, n (%)	13 (32.5)
Abdominal pain, n (%)	19 (47.5)
Pancreaticoduodenectomy, n (%)	10 (25)
Middle pancreatectomy, n (%)	1 (2.5)
Distal pancreatectomy, n (%)	23 (57.5)
DP/additional organ other than spleen, n (%)	11 (27.5)
Total pancreatectomy	3 (7.5)
Enucleation, n (%)	3 (7.5)
R1 surgical margins, n (%)	5 (12.5)
Complications, n (%)	15 (37.5)
Delayed gastric emptying	4 (10)
Pancreatic fistula	11 (27.5)
Abdominal abscess	4 (10)
Other infectious complications (wound infection, pneumonia, UTI)	3 (7.5)
Tumor size, cm, median (range)	3.5 (0.6–15)
Tumor type, n (%)	
Renal cell carcinoma	20 (50)
Ovarian adenocarcinoma	6 (15)
Colon adenocarcinoma	3 (7.5)
Sarcoma (chondrosarcoma, stomach leiomyosarcoma, malignant fibrous histiocytoma)	3 (7.5)
Malignant melanoma	2 (5)
Others (esophageal, gallbladder, adrenal cortical, fallopian, bladder, choriocarcinoma)	6 (15)

DP, distal pancreatectomy; UTI, urinary tract infection.

Table 2

Survival for the Various Malignancies after Metastasectomy

Primary tumor	Survival, y, median (range)
Renal	8.7 (1.2–12)
Ovarian	1.3 (0.05–2)
Colon	1.2 (0.5–5)
Sarcomas	0.6 (0.5–15.5)
Melanoma	Not reached

Table 3

Clinicopathologic Factors for Patients undergoing Metastatectomy for Renal Cell Cancer

	n = 20
Age, y, median	68.5
Female sex, n (%)	7 (35)
Right RCC, n (%)	11 (55)
Metastasis synchronous with the primary, n (%)	1 (5)
Solitary nodules, n (%)	15 (75)
Median size of the nodules, cm (range)	3 (0.8–12)
R1 margins, n (%)	4 (20)
LN metastases, n (%)	3/12 (25)
Median time to metastasectomy, y	8.7
Median follow-up after metastasectomy, y	3
Median survival, y	8.7
5-y Actuarial survival, %	61
LN, lymph node; RCC, renal cell cancer.	