

Clinical Features of Metastatic Tumors of the Pancreas in Korea: A Single-Center Study

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Background/Aims: The purpose of this study was to examine the clinical features of metastatic tumors of the pancreas (MTPs) in Korea. **Methods:** A total of 53 cases (31 males) of pathologically proven MTPs were collected. Clinicopathological characteristics and patient outcomes were evaluated. **Results:** The median age at the diagnosis of the MTP was 60 years. The median interval between the diagnoses of primary malignancy and MTP was 2.2 years. Primary malignancies were renal cell carcinoma (RCC) (n=14), gastric cancer (n=11), colorectal cancer (n=5), lymphoma (n=4), non-small cell lung cancer (n=3), gastrointestinal stromal tumor (n=2), melanoma (n=2), small cell lung cancer (n=2), gallbladder cancer (n=2), hepatocellular carcinoma (n=1), thymic carcinoma (n=1), liposarcoma (n=1), cholangiocarcinoma (n=1), osteosarcoma (n=1), breast cancer (n=1), duodenal cancer (n=1), and ovarian cancer (n=1). The median survival after the diagnosis of MTP was 23.1 months. Multivariate analysis showed that prolonged survival was associated with RCC as the primary malignancy, the patient being asymptomatic upon the diagnosis of MTP, the absence of extrapancreatic involvement, and surgery included in the treatment. **Conclusions:** MTPs can occur after a prolonged period from the primary diagnosis. RCC as the primary malignancy, the patient being asymptomatic upon the diagnosis of MTP, the absence of extrapancreatic involvement, and surgery included in the treatment are associated with better prognosis. (*Gut Liver* 2011;5:61-64)

Key Words: Pancreas; Neoplasms; Neoplasm metastasis; Renal cell carcinoma; Stomach neoplasms

INTRODUCTION

Metastatic tumors of the pancreas (MTPs) account for 3 to

16% of pancreatic malignancies. In most cases, they are part of a systemic metastasis,¹ hence the prognosis is poor.² MTPs are reported to occur with similar frequencies between men and women. They occur usually in the 6th decade.¹ Renal cell carcinoma (RCC), lung cancer, colorectal cancer, melanoma, and breast cancer are known to metastasize to the pancreas.²⁻⁴ Presenting symptoms or signs of MTPs can be abdominal pain, jaundice, diabetes, or acute pancreatitis.¹ In contrast to pancreatic ductal adenocarcinoma, aggressive surgical interventions in cases with metastasis confined to the pancreas are known to offer better prognosis, especially in RCC.³⁻⁵

A previous report by the authors reported 25 cases of pathologically confirmed MTPs in Korea.⁶ The purpose of this study is to evaluate the clinical features and prognosis of MTPs with updating the authors' experience in a single center. The current report evaluates 53 patients with pathologically confirmed MTPs over a period of 13 years.

MATERIALS AND METHODS

We collected 53 patients who were diagnosed as MTPs with pathological confirmation in Seoul National University Hospital from January of 1997 to December of 2009. Patients were excluded when direct invasion from the primary malignancy was confirmed on imaging or intraoperatively. Gender, primary malignancy, age at the diagnosis of primary malignancy, age at the diagnosis of MTP, symptoms or signs upon the diagnosis of MTP, time interval between the diagnoses of primary tumor and pancreatic metastasis, location of the pancreatic metastasis, number of pancreatic metastases, extrapancreatic involvement, treatment after the diagnosis of MTP, and survival after the diagnosis of MTP were evaluated. The endpoints of this study were patient death or March 31st, 2010. This retrospective study was carried out in accordance with the ethical guidelines

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of the Helsinki Declaration, revised in the 59th World Medical Association General Assembly in 2008. Informed consent was obtained from all patients prior to surgery.

Median survival was estimated using the Kaplan-Meier method. Factors associated with prolonged survival were determined using the log-rank test. For factors of age at primary tumor diagnosis, gender, and those associated with prolonged survival in univariate analysis at $p < 0.25$ were included as covariates in the Cox regression. Values are reported as median. Two-sided p -values of < 0.05 were considered statistically significant. All analyses were done using SPSS for Windows version 11.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Clinicopathological characteristics

Thirty-one patients were male, and 22 patients were female. The median age at the diagnosis of the primary malignancy was 53 (range, 23–76) years. The most common primary malignancies were RCC ($n=14$) and gastric cancer ($n=11$). The primary malignancies are summarized in Table 1. The median follow-up period after the diagnosis of MTP was 10.4 (range, 0–105.8) months.

The median age at the diagnosis of MTP was 60 (range, 25–76) years. MTPs were diagnosed synchronously in 15 patients (28.3%), 2 of whom were diagnosed on autopsy. The median interval between the diagnosis of primary malignancy and the di-

agnosis of MTP was 2.2 (range, 0–14.2) years. Of the 38 patients who were diagnosed metachronously, 22 were diagnosed during follow-up for the primary malignancy without any symptoms or signs. Eight patients presented with jaundice, 8 with abdominal pain, 4 with weight loss, 1 with upper GI bleeding, 1 with acute pancreatitis, and 3 laboratory abnormalities other than hyperbilirubinemia.

The locations of MTPs were head ($n=23$), body ($n=8$), tail ($n=14$), body and tail ($n=4$), head and tail ($n=1$), and diffuse involvement of the head, body, and tail ($n=3$). Forty-five patients had single lesions in the pancreas, and 8 patients (7 patients with RCC and 1 with lymphoma) had multiple pancreatic lesions. Extrapancreatic involvements of metastatic cancer were observed in 32 patients; the primary malignancies of these patients were RCC ($n=6$), gastric cancer ($n=6$), colorectal cancer ($n=4$), lymphoma ($n=3$), gastrointestinal stromal tumor ($n=2$), melanoma ($n=2$), small cell lung cancer ($n=2$), non-small cell lung cancer ($n=2$), liposarcoma ($n=1$), breast cancer ($n=1$), gallbladder cancer ($n=1$), duodenal cancer ($n=1$), and ovarian cancer ($n=1$).

2. Treatment and survival

After the diagnosis of MTP, 16 patients underwent chemotherapy, 15 surgery with chemotherapy, 11 surgery, 3 surgery and chemoradiation, 1 radiation therapy, 1 chemoradiation, and 6 palliative care. In 29 patients who had surgery included in their treatment, 14 underwent distal pancreatectomy, 11 pancreaticoduodenectomy, 2 median pancreatectomy, 1 palliative bypass, and 1 mass excision. Indications for surgery were isolated MTP in 10 cases, simultaneous pancreatic resection during surgery for primary tumor in 7, preoperative diagnosis of primary pancreatic cancer in 5, debulking of mass in 3, palliative procedure in 3, and preoperative diagnosis of primary duodenal tumor in 1. The median survival after the diagnosis of MTP estimated by the Kaplan-Meier method (excluding the 2 patients diagnosed on autopsy) was 23.1 months (Fig. 1).

Table 1. Primary Malignancy with Metastasis to the Pancreas

| Diagnosis | No. |
|--------------------------------|-----|
| RCC | 14 |
| Gastric cancer | 11 |
| Colorectal cancer | 5 |
| Lymphoma* | 4 |
| Non-small cell lung cancer | 3 |
| Gastrointestinal stromal tumor | 2 |
| Melanoma | 2 |
| Small cell lung cancer | 2 |
| Gallbladder cancer | 2 |
| Hepatocellular carcinoma | 1 |
| Thymic carcinoid | 1 |
| Liposarcoma | 1 |
| Cholangiocarcinoma | 1 |
| Osteosarcoma | 1 |
| Breast cancer | 1 |
| Duodenal cancer | 1 |
| Ovarian cancer | 1 |

RCC, renal cell carcinoma.

*Includes 2 cases of nasal type NK/T cell lymphoma, 1 case of gastric lymphoma, and 1 case of lymphoma of the liver.

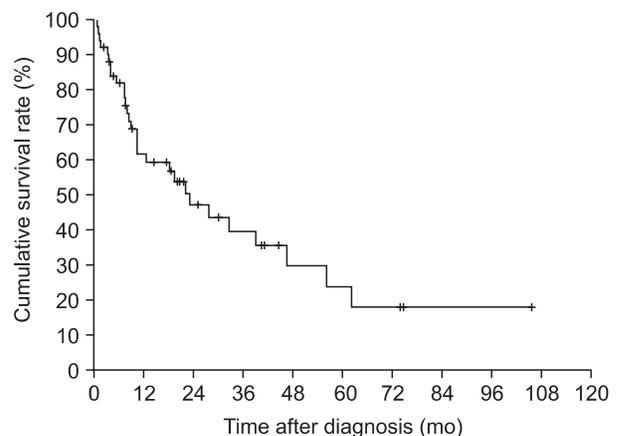


Fig. 1. Cumulative survival rate after the diagnosis of metastatic tumor of the pancreas estimated by the Kaplan-Meier method (two patients diagnosed on autopsy were excluded).

Table 2. Univariate Analysis of Factors Associated with Prolonged Survival after a Diagnosis of MTP (Two Patients Diagnosed on Autopsy Were Excluded)

| Factor | Median survival* | p-value |
|--|------------------|---------|
| Gender | | 0.052 |
| Male (n=30) | 12.6 | |
| Female (n=21) | 38.9 | |
| Primary malignancy | | 0.025 |
| RCC (n=14) | 56.1 | |
| Others (n=37) | 18.3 | |
| Age at the diagnosis of primary malignancy | | 0.173 |
| ≥55 yr (n=25) | 10.4 | |
| <55 yr (n=26) | 32.6 | |
| Involvement of the pancreatic head | | 0.861 |
| Yes (n=26) | 23.1 | |
| No (n=25) | 32.6 | |
| Symptoms or signs upon the diagnosis of the MTP | | 0.003 |
| Absent [†] (n=35) | 32.6 | |
| Present (n=16) | 7.6 | |
| Extrapancreatic involvement | | 0.002 |
| Yes (n=30) | 10.4 | |
| No (n=21) | 46.6 | |
| Surgery included in the treatment | | 0.004 |
| Yes (n=29) | 46.6 | |
| No (n=22) | 10.4 | |
| Interval between the diagnosis of primary malignancy and MTP | | 0.030 |
| ≥6 years (n=16) | 38.9 | |
| <6 years (n=35) | 10.4 | |

Results of log-rank test.

RCC, renal cell carcinoma; MTP, metastatic tumor of the pancreas.

*Value in months; [†]Includes the 15 patients whose MTPs were diagnosed synchronously.

Cumulative survival rates at 1, 2, 3, 4, and 5 years were 61.7%, 47.1%, 39.5%, 29.6%, and 23.7%, respectively.

On univariate analysis of survival using the log-rank test, RCC as the primary malignancy, symptoms of signs absent upon the diagnosis of the MTP (including the 15 patients whose MTPs were diagnosed synchronously), no extrapancreatic involvement, surgery included in the treatment, and interval between the diagnoses of primary malignancy and MTP ≥6 years were associated with prolonged survival (Table 2). On multivariate analysis, RCC as the primary malignancy, symptoms of signs absent upon the diagnosis of the MTP, no extrapancreatic involvement, and surgery included in the treatment were associated with prolonged survival. Age at the diagnosis of primary malignancy ≥55 years was associated with poor outcome (Table 3).

DISCUSSION

In this study, RCC and gastric cancer were the most common primary malignancies that metastasized to the pancreas. The median interval between the diagnoses of primary malignancy and MTP was 2.2 years. The median survival after the diagnosis of MTP was 23.1 months. Factors associated with prolonged survival were RCC as the primary malignancy, symptoms or signs absent upon the diagnosis of the MTP, no extrapancreatic involvement, and surgery included in the treatment. One interesting finding in our study was the high ratio of gastric cancer patients. Gastric cancer accounted for 20.8% of the patients, being second only to RCC. This may be attributed to the fact that gastric cancer is the most common cancer in Korea.⁷

Since most reports on MTPs are surgical series, there is little information available on extrapancreatic involvement of the primary malignancy, since these patients are more likely to be excluded from surgical candidates. In one report, 2 of 13 patients had extrapancreatic involvement.⁸ In our series, 32 of 53 patients (60.4%) had extrapancreatic involvement.

Multiple metastasis to the pancreas were detected in 8 patients (15.1%). Apart from 1 lymphoma patient who was diag-

Table 3. Multivariate Analysis of Factors Associated with Prolonged Survival after a Diagnosis of MTP (Two Patients Diagnosed on Autopsy Were Excluded)

| | HR | 95% CI | p-value |
|--|------|-----------|---------|
| Male gender | 1.93 | 0.80–4.63 | 0.142 |
| RCC as the primary malignancy | 0.11 | 0.03–0.41 | 0.001 |
| Age at the diagnosis of primary malignancy ≥55 yr | 2.86 | 1.16–7.05 | 0.023 |
| Symptoms or signs absent upon the diagnosis of the MTP* | 0.25 | 0.10–0.60 | 0.002 |
| No extrapancreatic involvement | 0.21 | 0.08–0.57 | 0.002 |
| Surgery included in the treatment | 0.33 | 0.13–0.81 | 0.016 |
| Interval between the diagnosis of the primary malignancy and MTP ≥6 yr | 0.44 | 0.16–1.23 | 0.119 |

HR, hazards ratio; CI, confidence interval; RCC, renal cell carcinoma; MTP, metastatic tumor of the pancreas.

*Includes the 15 patients whose MTPs were diagnosed synchronously.

nosed with MTP on autopsy, multiple metastases to the pancreas were detected in RCC patients only. In a literature review of isolated metastatic tumor to the pancreas from RCC, 39% had multiple lesions in the pancreas.⁹ They concluded that patients with multiple metastases to the pancreas should undergo radical resection if possible, since the outcome of these patients are not significantly poorer compared to those of patients with single metastasis.⁹ Four patients with RCC with multiple metastases to the pancreas but without extrapancreatic involvement underwent treatment including surgery, and they are still alive to this date.

Of the 17 patients who underwent surgery, 6 patients were initially diagnosed of having primary pancreatic or duodenal tumor. Z'graggen *et al.*⁴ reported that in 10 patients who underwent surgical extirpation for apparently isolated MTPs, 7 were initially misdiagnosed as primary pancreatic cancers. Although typical imaging features of RCC metastasis to the pancreas have been reported, it is still difficult to differentiate other metastatic tumors of the pancreas from primary pancreatic cancers. In such cases, endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration may aid in the accurate differentiation.¹⁰

MTPs may occur after a prolonged time after the diagnosis of the primary tumor,^{3-5,9} with reports of time interval longer than 30 years.¹¹ In our study, the longest interval was 14.2 years. It has been suggested that MTPs should be considered in patients with pancreatic lesion and history of malignancy, regardless of disease free interval, especially in patients who have an history of RCC.³

The prognosis of MTPs is generally poor, since in most cases they are a part of an advanced malignant disease.¹ However, in selected cases, especially RCC, surgical management of MTPs offer improved prognosis.^{3,8,9,11,12} In our study, the median survival after the diagnosis of MTP was 23.1 months. The median survival of RCC patients was better than that of with other malignancies differed significantly (56.1 months vs 18.3 months, $p=0.025$), which was a further supported by the results of multivariate analysis. A recent study of 49 patients with pancreatic resection of isolated pancreatic metastasis also showed that the median survival of 21 patients with pancreatic metastasis from RCC was 4.8 years and significantly better than that of pancreatic metastasis originating from other organs.¹³ In the present study, of the 14 patients who had RCC, 6 patients underwent treatment without surgery; the survival periods of these patients were 10.4, 18.6, 22.1, 23.1, 56.1, and 62.2 months, respectively. This may imply that some cases of RCC exhibit less aggressive tumor biology compared to other malignancies.

Our study has limitations. This is a retrospective study. The number of patients who had malignancies other than RCC or gastric cancer was small. The primary malignancies and treat-

ments were of heterogenous nature. Nevertheless, all cases were pathologically confirmed, and multivariable analysis of factors affecting survival were done.

In conclusion, MTPs may occur after a prolonged period from the primary diagnosis. The most common primary malignancies were RCC and gastric cancer in Korea. Patients with RCC as the primary tumor, without symptoms or signs upon the diagnosis of the MTP, without extrapancreatic involvement, and who have surgery included in their treatment may have prolonged survival.

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