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ORIGINAL ARTICLE – PANCREATIC TUMORS

Surgical Resection for Metastatic Tumors in the Pancreas: A Single-Center Experience and Systematic Review

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ABSTRACT

Background. Metastatic lesion to the pancreas accounts for approximately 2% of pancreatic neoplasms. There is no prospective, randomized or case-controlled study evaluating the role of pancreatic metastasectomy.

Methods. The PubMed, EMBASE, and Cochrane Library electronic databases were searched for studies published between January 1, 2001 and December 31, 2017. Studies with five or more patients who received pancreatic metastasectomy and data from our institution (29 patients) were included. The Kaplan–Meier method was used for survival analysis.

Results. A total of 414 patients from 20 institutions who underwent pancreatic resections were included. Of the reported 31 kinds of primary neoplasms, renal-cell carcinoma (RCC) comprised the most (54.3%). At the time of diagnosis, although 40.3% patients were asymptomatic, abdominal pain (34.8%) and jaundice (20.6%) were relatively common. As for surgical type, pancreatoduodenectomy, total pancreatectomy, distal pancreatectomy, and enucleation took up 37.9%, 11.4%, 43.5%, and 7.2% respectively. The mortality and morbidity rates were 1.4% and 48.3% respectively. Patients with symptoms at the time of diagnosis had significantly shorter survival compared with asymptomatic patients ($p = 0.017$). Those with RCC as primary tumor had significantly longer survival compared with non-RCC patients ($p < 0.001$). Positive margin also predicts worse prognosis ($p = 0.035$).

Conclusions. Pancreatic metastasectomy is safe and associated with acceptable short- and intermediate-term results. In the conditions of RCC as the primary tumor, being asymptomatic, or negative resection margin, a better prognosis after resection can be achieved.

Metastatic lesions to the pancreas are uncommon, only accounting for 2% of all pancreatic neoplasms.[1] These metastases can be divided into two clinicopathological types: a widespread systemic disease or an isolated lesion of pancreas. Unfortunately, most patients present widespread metastatic disease at the time of diagnosis.[2] A growing body of literature suggests that patients with metastatic colorectal cancer, renal cell carcinoma, melanoma, and neuroendocrine cancer have better prognosis when the metastases are resected.[3–6] Although most literature justifies metastasectomy, especially the resection of metastatic lesions of liver, lung, and brain, the effectiveness of pancreatic metastasectomy remains unclear. No prospective, randomized, or case-controlled study has evaluated the role of pancreatic metastasectomy, probably because of the rarity of this condition and the limited

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sample size. The majority of existing retrospective studies as well as case reports claim that comparing to nonoperative treatment, pancreatic metastasectomy has a trend to prolong survival.[7–11] So far, no evidence-based guideline for the management of this condition exists. In this study, we reviewed our institutional experience and performed a systematic review of the literature to ascertain the rationality of pancreatic metastasectomy.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were used in this review and the protocol was registered in the PROSPERO platform (record CRD 42018116593).[12]

Search Strategy

A literature search was performed in the PubMed, EMBASE, and Cochrane Library electronic databases. The keywords were combined using Boolean operators as follows: (pancreas AND (metastasis OR metastases) AND (surgery OR surgical OR resection OR pancreatectomy OR metastasectomy)). We also searched the clinical database from our institution, and 29 patients were identified.

Study Selection

Inclusion criteria were studies with five or more patients published between January 1, 2001 and December 31, 2017. Exclusion criteria were case reports, studies focusing on the palliative management, and review articles. When patient populations were duplicated or overlapping in different publications (according to authors, institutions, and years of publication), only the largest cohort was included. Studies in which some patients did not accept operations were included if the survival data for patients undergoing surgeries could be extracted separately.

Data Extraction and Statistical Analysis

Data extraction was performed independently by two reviewers (Q. Huang and C. Liu) and then crosschecked. Any corrections were made after agreement between the two reviewers. Data extracted included: the year of publication, first author, authors' institution and country, number of patients and their demographics, pathology of primary tumor, with or without symptoms, with or without lymph node metastasis, with or without vascular invasion, synchronous or metachronous with the primary disease, presence or absence of extra-pancreatic involvement, types of operations, positive or negative margin, mortality, morbidity, and survival data. Five-year survival was derived. Percentages and weighted means were used to summarize the patient, study, and outcomes. The Kaplan–Meier method was used for survival analysis. Differences were calculated by the log rank test. A p value < 0.05 was considered statistically significant. SPSS version 24.0 (SPSS Inc., Chicago, IL) was used for all statistical analyses. The methodological quality of the selected studies was assessed by the Methodological Index for NonRandomised Studies (MINORS) criteria.[13] MINORS assess these studies by eight items (12 items used in controlled studies), each of which is given a score of 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate).

RESULTS

A total of 943 reports were identified. Of these, 133 studies were excluded because of duplicates. After abstract review, 757 studies were excluded. Thirty-four studies were excluded after full text review, mainly because of small sample size. Also, two studies were excluded because of being written in other languages, three because they focused mainly on imageological diagnosis, and two because of identical publication. The remaining 19 studies met the criteria and were included for data extraction and analysis. The flowchart with each step of the selection process is presented in Fig. 1.

Pathological Characteristics

A total of 466 patients from 20 institutions (including 29 patients from our institution) were reviewed in this study (Table 1).[2,7–11,14–26] Among them, 414 had pancreatic metastasectomy; the remaining 52 received no surgery. The median follow-up was 24 (range 1–59) months.

Thirty-one kinds of primary neoplasms were reported to metastasize to the pancreas. Renal-cell carcinoma (RCC) (54.3%) comprised most primary tumors with metastases in the pancreas, which was consistent with literatures.[26,27] After renal-cell carcinoma, colorectal cancer (9.9%) was the second most common primary tumor. Besides these, there was little difference among the proportions of other pathological diagnoses, including sarcoma (4.3%), malignant melanoma (4.5%), lung cancer (5.4%), ovarian adenocarcinoma (4.5%), and gastric cancer (4.7%). The rest 12.4% consisted of 24 different kinds of tumors (Supplement Fig. 1).

Clinical Manifestation

Approximately 50% patients were asymptomatic at the time of diagnosis.[8,28] These patients often are detected

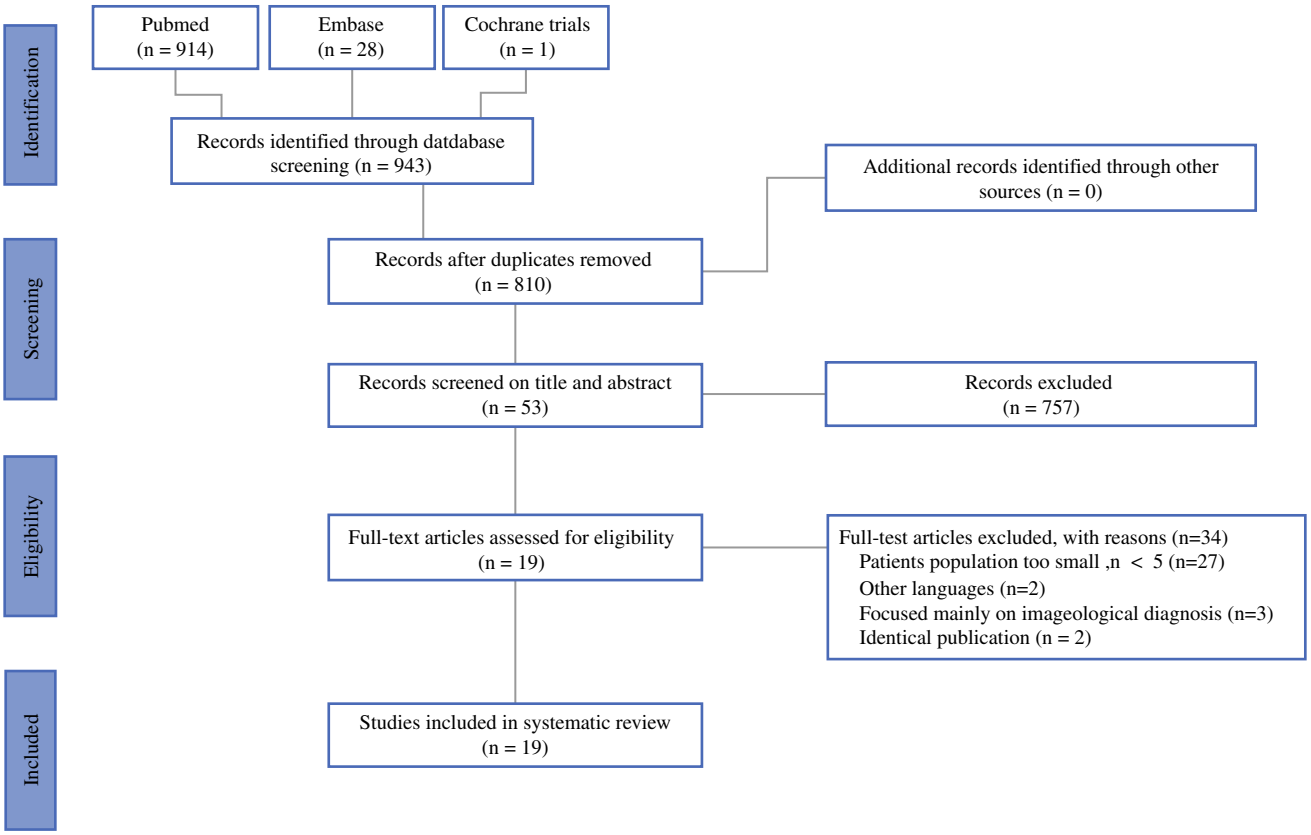

FIG. 1 Flowchart of study screening according to PRISMA guidelines

TABLE 1 Studies of pancreatic metastasectomy with five or more patients

Number	Author	Country	Year	No. of patients	MINORS score
1	Faure[14]	France	2001	8	8
2	Hiotis[15]	USA	2002	16	11
3	Law[16]	Canada	2003	14	9
4	Moussa[9]	France	2004	22	7
5	Crippa[10]	Italy	2006	13	9
6	Eidt[17]	Germany	2007	12	9
7	Varker[18]	USA	2007	29	10
8	Zerbi[8]	Italy	2008	23	10
9	Schauer[19]	Germany	2008	10	11
10	Sperti[20]	Italy	2009	9	11
11	Konstantinidis[2]	USA	2010	40	9
12	Masetti[21]	Italy	2010	9	12
13	You[22]	Korea	2011	11	10
14	Yoon[11]	Korea	2011	53	12
15	Alzahrani[7]	USA	2012	20	11
16	Yazbek[23]	France	2012	11	9
17	Niess[24]	Germany	2013	26	10
18	Moletta[25]	Italy	2014	13	11
19	Lee[26]	USA	2017	98	12
20	Our institution	People's Republic of China	2018	29	

during the follow-up after treatment of the primary tumors. Yet different kinds of symptoms, although nonspecific, may present. In this review, 13 of 19 studies provided individual patient data ($n = 184$).[7,9,10,14–17,19–24] At the time of diagnosis, asymptomatic patients were a large proportion (40.3%). Abdominal pain ($n = 64$, 34.8%), jaundice ($n = 38$, 20.6%), and upper gastrointestinal hemorrhage ($n = 17$, 9.2%) were the most frequent symptoms.[20,23,24]

Operative and Postoperative Details

The number of pancreatic metastasectomy has been growing owing to the declining mortality and morbidity over the years. Among 414 pancreatic metastasectomies included in this review, pancreatoduodenectomy (PD), total pancreatectomy (TP), distal pancreatectomy (DP), and enucleation were 37.9%, 11.4%, 43.5%, and 7.2% respectively (Table 2). In 119 cases (28.7%), resections of synchronized extrapancreatic metastases were performed. In these cases, liver (23.5%), colon/small bowel (21.0%), and omentum (12.6%) were the most common metastatic lesions got resected. We identified 58 cases of extrapancreatic metastasectomy with adequate details and found no statistically significant difference between the outcomes of those who underwent extrapancreatic resections and those who did not ($p = 0.261$).

TABLE 2 Operative and postoperative details

Operations	Number	LOS (days)
Whipple	157	36 (range 7–75)[24,25+]
TP	47	33 (range 14–52)[24,25+]
DP	180	32 (range 4–110)[24,25+]
Enu	30	
Other resections		
Liver	28	
Diaphragm	2	
PV/SMV resection	4	
Colon/small bowel	25	
Adrenal/kidney	14	
Uterus/fallopian tubes/ovaries	3	
Thyroid	1	
Stomach	11	
Lung/diaphragm	3	
Mediastinum	1	
Omentum	15	
Peritoneum	2	
Retroperitoneal resection	8	
Brain	2	

Whipple, pancreatoduodenectomy; *TP* total pancreatectomy; *DP* distal pancreatectomy; *Enu* enucleation; *LOS* length of stay; *IQR* interquartile range; *PV* portal vein; *SMV* superior mesenteric vein

[+]Include data from our institution

The overall mortality and morbidity rates were 1.4% and 48.3% respectively. Of the 7 cases who died within 30-day postoperatively, 5 primaries were RCC, 1 was ovarian cancer, and 1 was not recorded.[2,15,16,18,26] By reviewing selected data from 366 patients (including patients from our institution) with adequate information, we found the most frequent complications were pancreatic fistula ($n = 40$, 10.9%), abscesses ($n = 23$, 6.3%), new-onset diabetes ($n = 13$, 3.6%), and wound infection ($n = 11$, 3%).[2,8,10,14–20,22–24,26,28] Most cases required no major interventions.

The median length of hospital stay after PD, TP, and DP were comparable: 36, 33, and 32 days, respectively (Table 2). There was a significant difference between these outcomes and those in the Johns Hopkins Hospital, with length of hospital stay being 10, 8, and 8 days respectively.[26,28] This may be because of regional difference of clinical practice, considering that the former data were mainly from institutions in Europe and the latter were from the United States.

Survival Analysis

We identified 162 cases from 13 institutions (including our institution) that had adequate details of the pathological features (Table 3).[7,9,10,14,16,17,19,21–24,26] Features assessed included tumor size, lymph node involvement, and vascular invasion, which might be predictive of survival.

Patients with symptoms (Fig. 2a) at the time of diagnosis had significantly shorter survival compared with asymptomatic patients ($p = 0.003$). Patients whose primary tumors were RCC had significantly longer survival ($p < 0.001$) compared with non-RCC patients (Fig. 2b). Positive margin ($p = 0.035$) also predicts a worse prognosis (Fig. 2c). Besides these, other factors, including synchronous occurrence ($p = 0.117$), distal pancreatectomy ($p = 0.735$), complication ($p = 0.578$), extrapancreatic resection ($p = 0.221$), diameter ≥ 4 cm ($p = 0.146$), and gender ($p = 0.779$) showed no statistically significant difference.

Methodological Quality of Studies

No study in this review had a control group nor was performed prospectively. The 19 studies achieved a median MINORS score of 10/16 (range 7–12).

TABLE 3 Pathological diagnosis of patients

Primary tumor	N	Median age	Interval (months)	Tumor size (cm)	LN (%)	VI (%)	R0 (%)	MF (%)	Survival (months)	5-year survival
RCC	104[7,9,10,14,16,17,19,21–24]	64[7,9,10,14,16,19,21–24]	93.6[7,9,10,14,16,17,19,21,22,24]	3.1[16,17,22,24]	7.6[14,16,17,23,26]	24.5[22–24,26]	93.8[14,16,17,19,21,23,24,26]	39.6[14,16,19,21,22,24,26]	133.0[14,16,19,21,23,24,26]	72%
CRC	24[7,9,10,17,20–22,24]	59[7,9,10,20–22,24]	23[7,9,10,17,20,22,24,29]	3.25[17,22,24]	25.0[17,20,26]	5.9[20,24,26]	72.7[17,20,21]	50.0[9,10,20–22,24]	33.7[7,9,10,17,20,22,24]	46%
Sarcoma	10[21,22,24]	51[21,22,24]	20.4[21,22,24]	5.5[22,24]	28.4[26]	0.0[24,26]	62.5[21,22,24]	20.0[21,22,24]	63.4[22,24]	64%
MM	6[10,20,25]	47[10,25]	48[10,20,25]	5.0[20,25]	38.2[15,20]	49.6[15,25]	71.6[15,20,25]	0.0[15,18]	25.0[10,20,25]	33%
Lung cancer	8[15]	NR	14.4[15]	4.0[15]	63.0[15]	25.0[15]	100.0[15]	0.0[15,18]	39.6[15]	NR
OA	9[10]	53[10]	18[+10]	3.5[+]	26.8[15]	0.0[15]	46.2[15]	10.0[15]	38.0[10,15]	54%
Breast cancer	4[9,10]	NR	NR	NR	NR	NR	NR	NR	24[9,10]	0%
Gastric cancer	2[+]	35[+]	NR	7.5[+]	66.7[+]	33.3[+]	66.7[+]	0.0[+]	NR	0%

All outcomes in this table include data from our institution

RCC renal cell carcinoma; *CRC* colorectal cancer; *MM* malignant melanoma; *OA* ovarian adenocarcinoma; *LN* lymph node metastasis; *VI*, vascular invasion; *R0* margin-negative resection; *MF* multifocal tumor; *NR* data not reported

[+]Data from our institution only

Our Institutional Experiences

Details of our institutional experiences are summarized in supplement Table 1. The major complication rate in our institution was 10.3% (3/29), including two pancreatic fistulas (Grade B) and one abdominal bleeding. There are two possible explanations for the low morbidity rate. First, we are one of the largest pancreatic surgery centers in China with approximate 1000 pancreatic surgical cases per year. It is well known that the high-volume center has low morbidity rate in pancreatic surgery. Second, it is possible that minor complications, such as minor infection, were not recorded. Twenty-five of 29 patients (86.2%) were alive at the last follow-up. This might be because of the relatively short period of follow-up (median 24 months). The type of primary tumors was mostly ovarian cancer, which was quite different from the type of tumors reported in the literature. This might be because the department of gynaecology in our hospital had the largest ovarian cancer cases in Shanghai. Also, the extrapancreatic metastasis rate was higher (65.5%, 19/29) in our series compared with those reported in the literature. This might be because of the relatively high percentage of ovarian cancers as the primary tumors, and the extra-pancreatic lesion was mostly the omentum.

Renal-cell Carcinoma

Renal-cell carcinoma (RCC) is the most common kidney cancer in adults, which has a high survival rate up to 95%.[30–32] Unfortunately, 20–30% RCCs were metastatic at the time of diagnosis, and the 5-year survival rate of metastatic patients decreased to less than 30%.[33] With surgical resection, the 5-year survival rate of metastatic RCC can be improved largely compared with those untreated patients.[8,29,34] Metastatic RCC lesions usually occur in liver, lung, and bone. Pancreas is an uncommon metastatic site. Patients with RCC often have an indolent natural history and metastases occurring many years after primary resection are considered as specific manifestations of recurrent RCC. Fullarton and Burgoyne[35] reported the longest interval (27 years) from nephrectomy to the pancreatic metastases. The median interval from nephrectomy to the pancreatic metastases in our review was 93.6 months (range 5–288 months; synchronous cases were excluded).[19,24]

It is controversial whether routine resection of regional lymph nodes is necessary for pancreatic metastases from RCC. Faure et al.[14] regarded radical lymph node dissection as optional, because no positive lymph node was found. Law et al.[16] recommended a standard oncological pancreatic resection with routine regional lymph node resection since they identified one patient (7%) with a regional

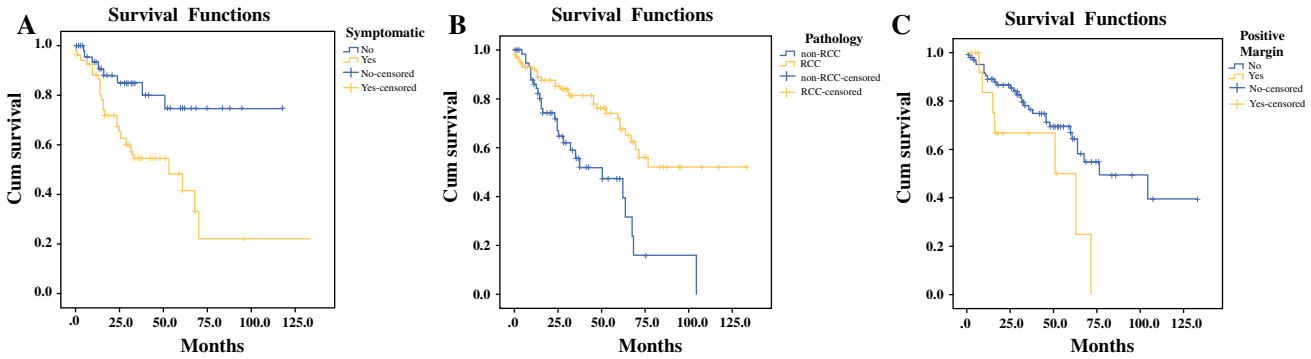

FIG. 2 **a** Patients who were asymptomatic at the time of diagnosis had longer survival compared with symptomatic patients. **b** Patients who underwent pancreatic resection for metastases from RCC had longer survival compared with non-RCC malignancies. **c** Patients with positive margin had worse prognosis compared with negative margin

peripancreatic lymph node metastasis. We found 8 patients (7.6%) with positive lymph node by reviewing 104 cases from literatures and data of our institution. Although Lee et al. pointed out that lymph node involvement did not affect outcomes of pancreatic metastases patients significantly, it would be reasonable to do a regional lymph node resection to get a better chance of R0 resection.[26]

In this study, those who had pancreatic metastasectomy from RCC showed a median 5-year survival rate of 72% (Table 3). The longest survival recorded was 133.8 months, and the patient was still alive at the end of follow-up.[16]

Colorectal Cancer

Approximately 20 percent of newly diagnosed colorectal cancer (CRC) patients have distant metastases, but they rarely metastasize to the pancreas.[36] According to Adsay et al.[37] 5 of 81 (6.2%) autopsy series of secondary tumors in pancreas had the primary location of colon. As for the time interval between diagnosis of colorectal cancer and pancreatic metastases, although Inagaki et al. reported a case of solitary metastasis to the pancreas from rectal carcinoma with an interval of 11 years, the median interval between the primary CRC and pancreatic metastases of our study was 23 months.[38]

Among the 46 cases of pancreatic metastases from CRC identified, 43 had primary cancer from the colon and 3 from the rectum. It is well known that CRC patients with resectable liver or lung metastases should have metastasectomy.[39] Although no such study has described the natural history of untreated patients with pancreatic metastases from CRC nor directly examined the role of pancreatic metastasectomy, we thought it was an indication for surgery. According to the literature, the 5-year survival rate after hepatic metastasectomy from CRC ranged from 28 to 58%.[40,41] In this study, those who had pancreatic metastasectomy from CRC showed a median 5-year survival rate of 46% (Table 3).

DISCUSSION

To the best of our knowledge, this is the most up-to-date systematic review of pancreatic metastasectomy with the largest sample sizes. The results show (1) RCC and CRC consisted the most common primary cancer of metastatic pancreatic tumors; (2) The mortality, morbidity, and survival of pancreatic metastasectomy are acceptable. (3) In the conditions of RCC as the primary tumor, being asymptomatic, or negative resection margin, a better prognosis after resection can be achieved.

Considering the obscure symptoms and the long median interval (93.6 months in this study) between the diagnosis of primary RCC and pancreatic metastases, a long-term follow-up is highly recommended, even for those who were recurrent-free for more than 5 years. Routine surveillance imaging by CT scans might be the most effective way to identify metastatic lesions. In addition, almost all lesions can be characterized and staged with CT scans, and it is easier to detect metastases when multifocal lesions occur with history of malignancies.[17,26] Pancreatic metastases can present as hypervascular or hypovascular masses in plain scan CT and often appear enhanced on arterial phase of a contrast-enhanced CT.[10,42] It is sometimes difficult to distinguish primary tumors and metastatic ones in the pancreas.[43,44] History of malignancy can provide some clues.

Although a lot of the literature have demonstrated that surgeries of pancreatic metastases from RCC could tend to improve survival and quality of life, a study involving 103 patients retrospectively compared survival of resected and unresected patients with pancreatic metastases from RCC, and it turned out that resection did not statistically prolong survival compared with tyrosine kinase inhibitor therapy.[45] Thus, it is reasonable to implement tyrosine kinase

inhibitor therapy in patients who cannot receive surgeries due to various reasons or patients who have high risk for postoperative complications. Motzer et al.[46] proposed to stratify patients with metastatic RCC into three groups by using a prognostic score model with five prognostic factors. This prognostic score was recently validated and modified by Mekhail et al.[47] We could not verify this stratification due to lack of data in this study, but it could be taken into consideration that this may help screen appropriate patients to receive different treatments. The better prognosis of renal cell cancer is well-known and demonstrated by many previous authors and stressed by the only one published meta-analysis.[48] Similar to findings reported in the literature, our results showed patients with primary tumors of RCC had the longest median survival. Moreover, we found that longer survival is related to being asymptomatic at the time of diagnosis and negative resection margin.

Although few statistically significant differences were found, we believed several selection criteria for pancreatic metastasectomy should be recommended, including primary cancer types associated with good prognosis, primary cancer site control, resectable metastases, and patients' tolerance for pancreatectomy. Therefore, the decision of pancreatic metastasectomy should be carefully and systematically made. Because literature showed that patients at high-volume centers usually had improved perioperative outcomes and better overall survival, it is reasonable for patients with metastatic pancreatic tumors to get treated in a high-volume center.[49]

CONCLUSIONS

Metastatic tumors of the pancreas can occur after a prolonged period from the primary diagnoses. Routine surveillance imaging by CT scans might be the most effective way to identify pancreatic metastatic lesions. The mortality, morbidity, and survival of pancreatic metastasectomy are acceptable. In the conditions of RCC as the primary tumor, being asymptomatic, or negative resection margin, a better prognosis after resection can be achieved.

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DISCLOSURE None.

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