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REVIEW

Metastatic tumors to the pancreas: a systematic review and meta-analysis

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ABSTRACT

INTRODUCTION: Metastases to the pancreas from other primary tumors are increasingly recognized in clinical practice, but the real role of surgery remains unclear. This study was designated to evaluate by a meta-analytic approach the results of surgical treatment for the most common malignancies metastasizing to the pancreas.

EVIDENCE ACQUISITION: MEDLINE, PubMED, Scopus and Web of Sciences were searched from January 2000 to December 2015. Studies reporting postoperative complications, postoperative mortality, disease-free and overall survival of patients undergoing resection for secondary tumours of the pancreas, were included.

EVIDENCE SYNTHESIS: Fourteen publication with 281 patients met the inclusion criteria and were subjected to the analysis. Operative morbidity and mortality were 34% and 1.3% respectively. Pancreatic resection for renal cell cancer showed better survival compared to other non-renal cell cancer (ratio of mean 1.83; 95% CI: 1.42-2.36, I^2=74.52%, P<0.001). Disease-free interval was longer for metastatic renal cell carcinoma patients (mean difference 6.36, 95% CI: 3.803-8.912 years, I^2=76:54%, P<0.001). A meta-regression was used to correlate the two endpoints and showed that a longer DFI is associated to a longer survival.

CONCLUSIONS: Pancreatic resection for metastasis should be reserved to patients in good health conditions, with isolated disease from renal cell cancer. For other types of tumor, surgery should be performed only in individual basis. There is a need of studies evaluating the role of chemotherapy in the neoadjuvant setting or the best sequential use of multimodality treatment (targeted therapy, radiotherapy, surgery, etc.).

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Key words: Meta-analysis - Neoplasm metastasis - Pancreatic neoplasms - Pancreatectomy - Renal cell carcinoma.

Introduction

Secondary tumors of the pancreas are rare, approaching to 2% of pancreatic masses,[1] whereas in autoptic series, pancreatic metastases are identified in up to 15% of patients with malignant disease.[2] A wide range of malignant tumors have been found to metastasize to the pancreas and the most frequent primary neoplasm were cancer of kidney, breast, colon, skin, lung and sarcoma.[3] Pancreatic metastases occur in two different clinical settings either as one manifestation in widespread disease or, less frequently (2%), as an isolated mass of the pancreas.[4] In recent years, the widespread use of imaging techniques in asymptomatic patients resulted in increasing number of patients with isolated pancreatic metastasis and in number of pancreatectomies performed in high volume centers.[5] Several data show that pancreatic surgery is safe and feasible in high-volume clinical centers, making surgical resec-

tion an acceptable indication also in pancreatic secondary lesions.[6-8] However, given the rarity of pancreatic metastases, and the lack of comparative studies between patients who undergo surgical resection and patients who undergo non-operative management, the role of surgery for secondary pancreatic malignancies is still unclear. It is also important to define which type of neoplasm may benefit from pancreatic resection. The aim of the present study was to perform a systematic review and meta-analysis to evaluate the results of pancreatic resection for the most common metastatic tumors to the pancreas.

Evidence acquisition

The published literature was systematically searched using PubMed, Scopus, Web of Science, and MEDLINE for studies published from January 2000 to December 2015. The following MeSH terms were used in multiple combinations: "pancreatic neoplasms/surgery", "pancreatic neoplasms/secondary", "pancreatic metastasis", "pancreatic neoplasms/therapy", "pancreatectomy", "pancreaticoduodenectomy", "distal pancreatectomy", "neoplasms metastasis". The related article function was used. All articles included in this study were used to broaden the search and all abstracts, studies and citations obtained were reviewed. Only case series comparing renal cell cancer (mRCC) and metastases from other tumors (mNRCC) were included in this analysis. The references of all studies included were screened for any potentially relevant studies. Only articles published in English language were included. Studies were excluded from the analysis if: 1) the sample size was too small (<7 patients); 2) the sample size for each group was <2 patients; 3) the outcome and parameters of interest were not clearly reported; and 4) the required information was impossible to extract from the published results. The choice of articles included in this study was in accordance with QUORUM (Quality of Reporting of Meta-analysis).[9] Each study was independently evaluated by 2 reviewers (G.P. and A.B.) for inclusion or exclusion from the meta-analysis. Title, first author, year of publication, characteristics of the study population, study design, number of patients who underwent surgery resection, type of primary neoplasm, perioperative morbidity and mortality, disease-free interval (DFI: time from resection of primary tumor to the onset of pancreatic metastasis) and overall survival after pancreatic resection were extracted from each study. Results are summarized in Table I. Two meta-analysis were carried out: the first focusing on overall survival (14 studies included) and the second on the DFI (10 studies included).

TABLE I.—*General and clinical data of all case series.*

First author	Year	Country	Study design	N. patient	N. RCC	N. other tumors	Median age (years)
Crippa *et al*.[12]	2006	Italy	Retrospective	11	5	6	59 (36-79)
Mourra *et al*.[13]	2010	France	Retrospective	12	8	4	60.8 (23-74)
Kostantinidis *et al*.[14]	2010	USA	Retrospective	40	20	20	62 (ND)
Niess *et al*.[15]	2013	Germany	Retrospective	26	16	10	65 (40-79)
Masetti *et al*.[16]	2010	Italy	Retrospective	9	6	3	61 (36-75)
Reddy *et al*.[17]	2008	USA	Retrospective	49	21	28	60 (47-69)
Eidt *et al*.[18]	2007	Germany	Retrospective	12	7	5	64 (55-70)
Yoon *et al*.[19]	2011	Korea	Retrospective	53	14	39	60 (25-76)
Hiotis *et al*.[20]	2002	USA	Retrospective	16	10	6	63 (39-81)
Redmond *et al*.[21]	2014	Ireland	Retrospective	7	3	4	61 (49-78)
Moussa *et al*.[22]	2004	France	Retrospective	10	7	3	60 (35-67)
You *et al*.[23]	2011	Korea	Retrospective	11	7	4	54 (35-75)
Jarufe *et al*.[24]	2005	UK	Retrospective	13	7	6	62 (40-73)
Le Borgne *et al*.[25]	2000	France	Retrospective	12	5	7	52 (33-72)
Total				281	136	145	

RCC: renal cell carcinoma.

Where missing, the median survival time and corresponding range were extrapolated from the available Kaplan-Meier plots. Since all articles used in this analysis report only the size of the study groups without standard errors, all median survival times were transformed into means and variances according to Hozo *et al.*[10] The survival data were pooled for analysis of either the mean difference (MD) or of the log ratio of means (ROM). In order to evaluate the between-study heterogeneity, a homogeneity test based on the Q statistic was performed. Where significant at 0.01 level, the summary effect, with corresponding 95% confidence interval, was obtained from a random-effects model. A cumulative meta-analysis was furthermore carried out to assess the stability of the pooled endpoint estimate. Meta-regression was used to correlate the two endpoints used. Publication bias was assessed by asymmetry of funnel plots. All the analyses were carried out using R Statistical Software v.3.2.3.[11]

Evidence synthesis

Studies selection and search strategy were showed in the quorum flow chart,[9] as reported in Figure 1. The preliminary literature search showed 659 studies matching the initial search criteria. After screening, 83 studies reporting metastases to the pancreas were evaluated: 69 articles were selected for full text review. There were 23 case series and 46 case reports reporting only metastasis from renal cell carcinoma. From the case series 14 have more than 7 patients with sufficient details to be included in the meta-analysis evaluating the long term survival, for a total of 281 patients with secondary neoplasm to the pancreas.[12-25] Four of the included studies, did not reported the DFI so only 10 studies were evaluated for the meta-analysis regarding the disease free interval. All were retrospective studies. General details of the studies are reported in Table I. There were 136 pancreatic mRCC, while 145 patients had pancreatic mNRCC: colon cancer (N.=24), melanoma (N.=16), lung cancer (N.=16), sarcoma (N.=13), ovary (12), gastric (N.=11), gallbladder (N.=11), breast cancer (N.=8),

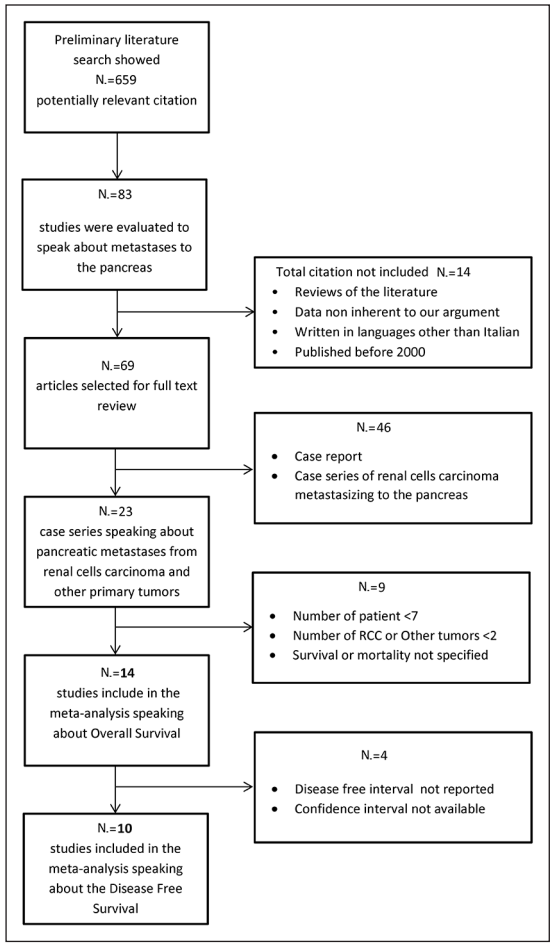

Figure 1.—Flow chart reporting the results of a systematic search of the literature according to the QUORUM statement.

TABLE II.—*Mortality and morbidity rates.*

First author	Overall morbidity	Overall mortality
Crippa *et al.*[12]	18.8%	0%
Mourra *et al.*[13]	8.3%	0%
Kostantinidis *et al.*[14]	37.5%	2.5%
Niess *et al.*[15]	35%	0%
Masetti *et al.*[16]	22.2%	0%
Reddy *et al.*[17]	46.9%	0%
Eidt *et al.*[18]	25%	0%
Yoon *et al.*[19]	ND	ND
Hiotis *et al.*[20]	25%	6%
Redmond *et al.*[21]	42.9%	0%
Moussa *et al.*[22]	ND	0%
You *et al.*[23]	27.3%	0%
Jarufe *et al.*[24]	46.2%	7.7%
Le Borgne *et al.*[25]	ND	0%
Total	34%	1.3%

ND: not defined.

TABLE III.—*Disease-free survival and outcomes following pancreatic surgery.*

First author	Overall median survival months (range)	RCC, median survival months (range)	Other tumors, median survival months (range)	Overall DFI months (range)	RCC DFI months (range)	Other tumors DFI months (range)
Crippa *et al*.[12]	26 (13-95)	32 (16-95)	19 (13-38)	36 (5-192)	66 (22-192)	33.5 (5-84)
Mourra *et al*.[13]	20 (9-84)	38 (9-84)	15 (9-20)	102 (0-312)	162 (48-252)	9.5 (0-84)
Kostantinidis *et al*.[14]	20.5 (6-185)	104.4 (14-144)	15.6 (0.6-186)	NR	NR	NR
Niess *et al*.[15]	63 (37.8-88.1)	54.7 (4-76)	49.6 (7-69)	63 (0-288)	98 (0-288)	57 (0-148)
Masetti *et al*.[16]	63 (47-79)	70 (6-134.4)	20 (0-130.8)	82.8 (36-132)	96 (60-144)	36 (15.6-57.6)
Reddy *et al*.[17]	44.4 (10-219.6)	57.6 (4.2-219.6)	28.8 (10.8-38.4)	57.6 (0.53-339.6)	NR	NR
Eidt *et al*.[18]	51 (5-105)	52 (5-86)	30 (12-105)	144 (12-240)	156 (108-240)	48 (12-168)
Yoon *et al*.[19]	23.1 (1-108)	56.1 (1-108)	18.3 (1-108)	26 (0-170)	NR	NR
Hiotis *et al*.[20]	39 (0-80.4)	57.6 (0-80.4)	16.8 (0-36)	90 (12-288)	109 (48-288)	51.6 (12-228)
Redmond *et al*.[21]	49 (17-76)	62 (49-76)	36 (17-69)	33 (15-281)	189 (15-281)	20.5 (15-281)
Moussa *et al*.[22]	25 (3-118)	45 (3-118)	7 (5-19)	85.5 (2-148)	102 (2-148)	45 (2-148)
You *et al*.[23]	34 (7-69)	34 (7-69)	16.5 (11-30)	51 (14-180)	64 (14-180)	50.5 (14-180)
Jarufe *et al*.[24]	31.8 (1-50)	30.5 (10-35)	26.4 (1-50)	NR	NR	ND
Le Borgne *et al*.[25]	12 (2-127)	18 (12-53)	12 (2-127)	66 (0-156)	7 (0-156)	5 (0-96)

RCC: renal cell carcinoma; DFI: disease-free interval; NR: not reported; ND: not defined.

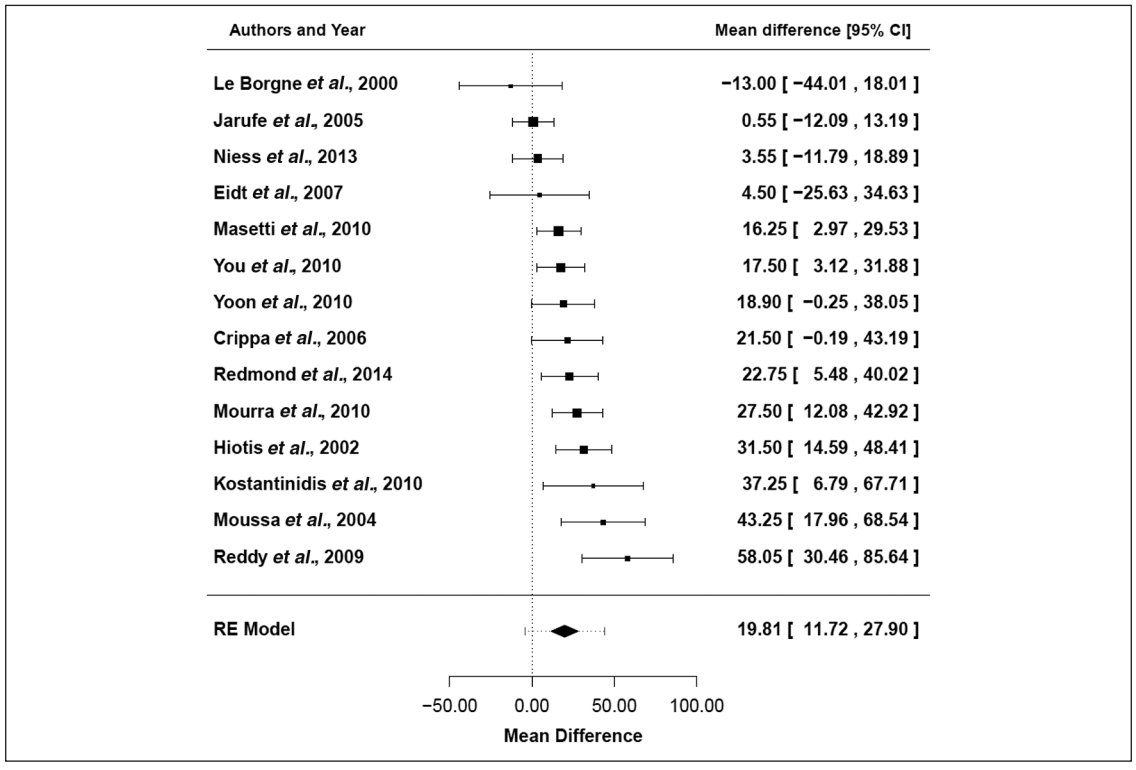

Figure 2.—Forest plot for mean difference of overall survival.

leiomyosarcoma (N.=6), and then, other very rare tumors (N.=28). Patients with primary renal cell carcinoma were evaluated separately from all the other primary tumors. Median age of the patients was not statistically different among studies. All patients underwent pancreatic resection: overall morbidity rate was 34.5% (range 8.3-46.9%) with a mortality rate of 1.3% (range 0-7.7%) (Table II). The results of the meta-analysis are summarized in

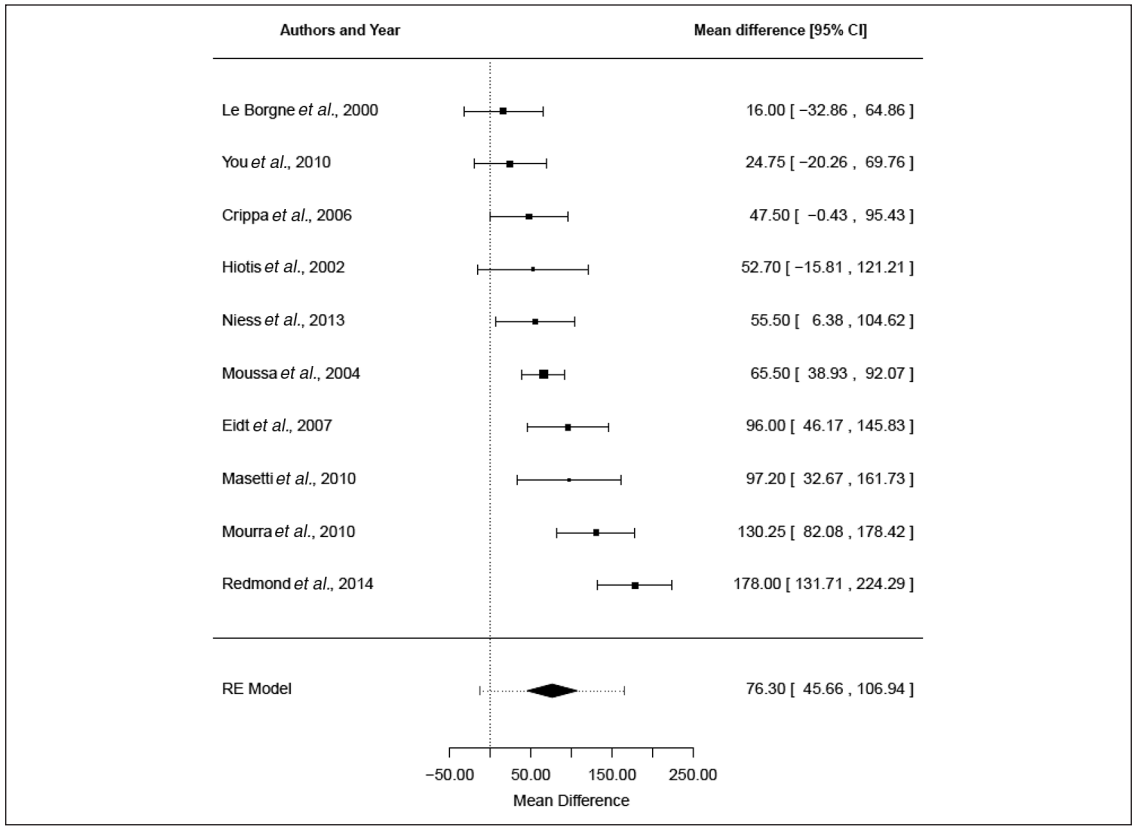

Figure 3.—Forest plot for mean difference of disease-free interval.

Table III. Overall survival was significantly better in patients who underwent surgery for mRCC compared to patients with mNRCC (ROM=1.83; 95% CI: 1.42-2.36, I^2=74.52%, P<0.001). The survival benefit for patients who underwent surgery for mRCC is approximately 20 months (MD=19.81; 95% CI: 11.72-27.90, I^2=60.82%, P<0.001), as shown in Figure 2. The cumulative meta-analysis demonstrated that the overall survival benefit after pancreatic resection for metastatic RCC settles very quickly. The disease-free interval of the mRCC group significantly exceeded the DFI of the mNRCC patients (ROM=2.993; 95% CI: 1.78-4.83, I^2=84.78%, P<0.001). In particular, the disease free interval of mRCC patients is 6 years longer (MD=6.36, 95% CI: 3.803-8.912 years, I^2=76:54%, P<0.001) than for the mNRCC patients (Figure 3). The meta-regression furthermore revealed that, with the exception of three studies,[15, 18, 25] a longer DFI is associated with a longer survival. All funnel plots provided no evidence of publication bias (Figures 4, 5).

Discussion

Pancreatic metastasis from other primary tumors are increasingly recognized in clinical practice, and may represent a problem for surgeons and oncologists. Some questions may arise: 1) is surgery of metastatic tumors worthwhile?; 2) which type of tumor might benefit from surgical resection?; 3) which one is the optimal treatment: surgery or chemotherapy? We tried to answer the first two questions with a systematic review of the literature and meta-analysis of papers dealing with metastatic tumors to the pancreas. We analyzed 14 case series and compared the results of surgical treatment of patients with metastatic RCC versus patients with pancreatic metastasis

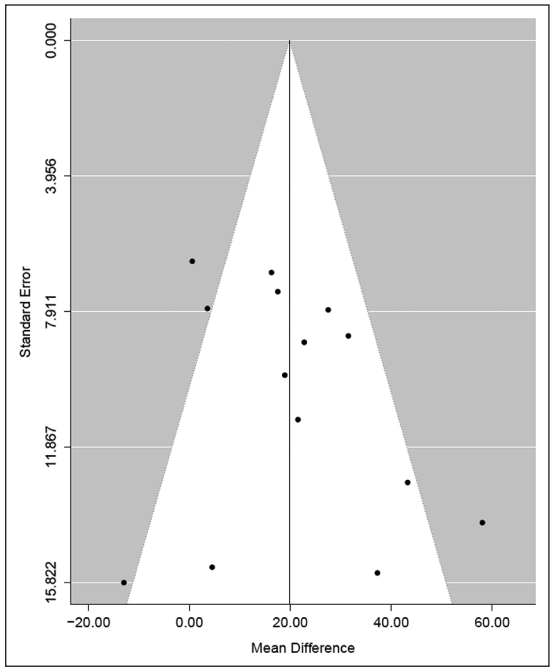

Figure 4.—Funnel plot for mean difference of overall survival.

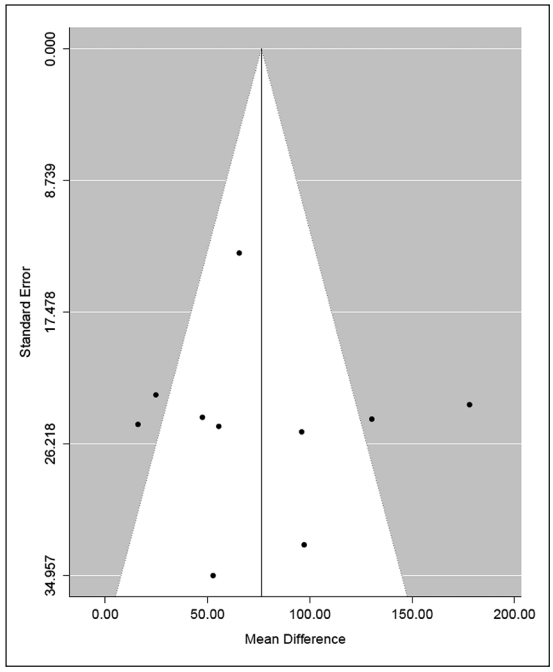

Figure 5.—Funnel plot for mean difference of disease-free interval.

from other tumors. The results of our study confirm that pancreatic resection for metastasis was associated with acceptable morbidity and low mortality rate (1.3%), resembling to the same results obtained after surgery for the most common primary carcinoma of the pancreas. So, surgical treatment of pancreatic metastasis appears safe and feasible, with low surgical risk in specialized hands. Our meta-analysis shows that disease-free interval was significantly longer in the mRCC group, and this finding is well known, since metastasis from RCC are frequently the only metastatic site and they typically occur a long time after nephrectomy.[1, 26] They may be the initial presentation of the disease or they can be an occasional asymptomatic finding during follow-up:[27] this underlines the need for a long follow-up (>10 years) in patients with RCC. We also found that overall survival of patients with mRCC was significantly longer compared to the survival of patients with other metastatic tumors. Furthermore, there was a trend of association between long disease-free interval and overall survival after metastasis resection, suggesting a less aggressive biology of mRCC compared to other tumors. Outcomes following pancreatic resection of mRCC have been largely favorable. In a systematic review of the literature with a pooled analysis of all studies, Adler *et al*.[28] reported a median survival of 50.2 months (range 26-78 months) after pancreatic resection, with an overall one-year survival of 86.81% and a 5-year survival of 50.02%. Masetti *et al.*[16] reported a median survival of 72 months for surgically treated patients, while patients who did not undergo pancreatic resection had a median survival of only 10 months. Pancreatic metastases from RCC seems to have a better prognosis when compared with secondary lesions from other primary malignancies, even if there is a lack of studies in literature directly comparing clinical outcome of these two different entities.[28] Based on the results of previous surgical series and our meta-analysis, resection seems to be the best option for improving the long-term survival of patients with an isolated pancreatic

lesion. Our results clearly demonstrate that survival of mRCC patients is definitely better than the outcome of patients with metastasis of other malignancy, confirming that mRCC is the optimal indication for surgical treatment. Surgery for other tumors seems to be reserved on individual basis, mostly for palliative intent.

Finally, the third question arises since from 2005 when new drugs have been approved by the US Food and Drug Administration for mRCC: the multitargeted tyrosine kinase inhibitors (sunitinib, sorafenib), the mammalian target of rapamycin (mTOR) pathway inhibitors (everolimus, temsirolimu) and the anti-vascular endothelial growth factor (VEGF) antibody (bevacizumab).[29] With the availability of different therapeutic agents, patients with mRCC can be in principle treated over the long term by the sequential use of the approved substances.[30] Recently, an Italian multicentre, retrospective study compared survival of resected versus unresected patients in a large cohort of patients (N.=103) with metastases to the pancreas from renal cell cancer. Surgical resection did not improve survival in comparison with tyrosine kinase inhibitors, but surgery showed the highest possibility for disease-free survival in patients with isolated pancreatic metastasis.[31] Unfortunatly, it is very difficult to compare results of surgical and non-surgical treatment of mRCC, because there is a lack of prospective studies on this topic.[32]

There are some limitations in our study. First, the data utilized included only retrospective studies with a potential selection bias; it is not based on individual patient data which makes not feasible to retrieve data about the corresponding end-points from all studies; the high heterogeneity we observed in our meta-analysis may be due to non-homogeneous types or quite different tumors included.

Conclusions

Surgical treatment for metastatic tumors to the pancreas may be offered safely to selected patients with isolated or limited disease. However, there are evidences that benefit of resection in term of prolonged survival is surely obtained for isolated metastases from renal cell cancer. For other types of tumor, the indication of surgery is made only on individual basis.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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