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EDITORIAL

Pancreatic metastases from renal cell carcinoma: The state of the art

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Abstract

Pancreatic metastases are rare, with a reported incidence varying from 1.6% to 11% in autopsy studies of patients with advanced malignancy. In clinical series, the frequency of pancreatic metastases ranges from 2% to 5% of all pancreatic malignant tumors. However, the pancreas is an elective site for metastases from carcinoma of the kidney and this peculiarity has been reported by several studies. The epidemiology, clinical presentation, and treatment of pancreatic metastases from renal cell carcinoma are known from single-institution case reports and literature reviews. There is currently very limited experience with the surgical resection of isolated pancreatic metastasis, and the role of surgery in the management of these patients has not been clearly defined. In fact, for many years pancreatic resections were associated with high rates of morbidity and mortality, and metastatic disease to the pancreas was considered to be a terminal-stage condition. More recently, a significant reduction in the operative risk following major pancreatic surgery has been demonstrated, thus extending the indication for these operations to patients with metastatic disease.

Key words: Pancreatic metastases; Renal cell carcinoma; Pancreatic surgery; Prognostic factors; Therapeutic approach; Radiological findings

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INTRODUCTION

Renal cell carcinoma (RCC) remains an important cause of cancer death in the United States, with an estimated 58 240 new cases and approximately 13 040 deaths in 2010[1].

The natural history of RCC is characterized by a high 5-year survival (up to 95%) when the tumor is limited to the kidney (stage 1)[2-4]. Among patients with RCC, 20% to 30% have metastases at presentation, and up to 40%-50% will develop widespread metastatic disease after nephrectomy. The 5-year survival rate is < 10%-15% once metastases have spread[5,6].

Pancreatic metastases are rare, with a reported incidence varying from 1.6% to 11% in autopsy studies of patients with advanced malignancy[7,8]. In clinical series, the frequency of pancreatic metastases ranges from 2% to 5% of all pancreatic malignant tumors[9-12].

The tumors that metastasize most commonly to the pancreas are RCC, lung cancer (adenocarcinoma and non-small cell lung carcinoma), lobular breast carcinoma, and colorectal adenocarcinoma, followed by melanoma, soft-tissue sarcoma (leiomyosarcoma), and a large number of other neoplasms[7,8,13-19].

However, the pancreas is an elective site for metastases from carcinoma of the kidney and this peculiarity has been reported by several studies[11,19-27]. Pancreatic metastases from RCC are frequently the only metastatic site and they typically occur a long time after nephrectomy[20,23,26].

MECHANISM OF DISEASE

According to Sellner *et al*[23], local lymphogenous or local venous spread through abnormal lymphatic or venous communications between the RCC and the pancreas[11,21,28] cannot play an important role, because this would fail to explain the lack of relationship between the site of isolated pancreatic metastases and the side affected by the primary tumor: i.e., the left or right kidney. The localization anywhere in the pancreas irrespective of the site of the RCC argues, instead, in favor of a hematogenous systemic spread. However, a systemic spread would not explain the discrepancy between the relative frequency of multiple pancreatic metastases and the absence of metastases to other organs. The most likely explanation for this unique behavior of isolated pancreatic metastases would seem to lie in the special biology of the tumor. Tumor cells apparently have a high affinity for the parenchyma of the pancreas and only there do they find the conditions they need to mature to manifest metastases. The high affinity of some renal cancer cells for the parenchyma of the pancreas is supported by some reports[23] of metachronous late metastases which again occurred solely in the residual pancreas[11,22]. The results of basic research, which is slowly unraveling the local biochemical mechanisms that underlie the development of metastases, are promising, so it is hoped that the biochemical causes of the unique spreading pattern of some RCC will perhaps be understood one day[29].

CLINICAL CHARACTERISTICS

As with primary pancreatic cancer, the early signs and symptoms of isolated pancreatic metastases are often non-specific and subtle. Isolated pancreatic metastases are often found with routine surveillance imaging for primary lesions or as an incidental finding on imaging done for an unrelated indication.

Pancreatic metastasis of RCC generally occurs in the seventh decade of life and is usually asymptomatic[14,15,30], although cases of abdominal pain, gastrointestinal bleeding caused by duodenal involvement, weight loss, jaundice, and pancreatitis due to pancreatic duct obstruction have been described[14,15,26,31].

Most of the studies reviewed report mean time intervals greater than 10 years, and a period as long as 32.7 years has been described[12,19,21-24,26,32]. In fact, renal carcinoma is the primary tumor that metastasizes to the pancreas following the greatest disease-free interval. This singular feature of RCC makes long-term follow-up essential in these patients.

Multiple lesions throughout the pancreatic gland have been more frequently detected in patients with RCC than in those with other primary tumors. Other single-center series reported similar frequencies of multifocality with respect to pancreatic RCC metastases, ranging from 20% to 45%[12,22,23,26,27,33,34]. In the review by Sellner *et al*[23], multiple lesions occurred in 39% of the 187 patients. This issue has important clinical implications: surgical treatment of patients with suspected pancreatic metastases from RCC must take into account the high probability that the patient will have more than one pancreatic lesion.

In a recent review by Masetti *et al*[35], univariate survival analyses conducted in a subgroup of patients with RCC metastases (n = 157), with a median follow-up of 24 mo (range 1 to 134 mo), showed that the factors associated with worse survival were symptoms at diagnosis, and a disease-free interval less than 2 years in patients with metachronous lesions.

RADIOLOGICAL FINDINGS

Computed tomography and magnetic resonance imaging

The diagnosis of pancreatic metastasis is usually made on radiological or endoscopic criteria, since most patients do not present related symptoms.

The disparity in prognosis and management of patients with primary and secondary pancreatic tumors, as well as the fact that in very selected cases a radical surgical resection can be considered as treatment of pancreatic metastases and achieve prolonged survival, underline the importance of detection and characterization of these lesions by computed tomography (CT) and magnetic resonance imaging (MRI)[9,24,36].

Identifying the sites and extent of the metastatic lesions within the pancreas helps determine the feasibility and extent of pancreatic surgery.

There is comparatively little difficulty in identifying large lesions within the pancreas when using a standard CT technique because they typically deform the contour of the pancreas. Small lesions, however, may be easily missed. The CT evaluation should be performed with

a multidetector CT, a high rate of intravenous contrast media injection (3-5 mL/s) and scanning during the arterial (20 s delay) and portal (50-60 s delay) phases. The MR evaluation should be performed with a 1.5 or 3 T scanner with T1 and T2 weighted sequences, without and with contrast media injection at dynamic acquisition in arterial, portal and venous phases.

The growing use of imaging techniques, in particular of CT in the periodic follow-up of oncological patients, allows earlier detection of small pancreatic metastases, and in most cases the oncological background and existence of previous follow-up permit a correct diagnosis. Moreover, in controversial cases, CT can also be considered as an important tool in providing guidance to biopsy in order to obtain a definitive diagnosis[9,10,36,37].

Imaging features of metastatic pancreatic tumors point to their primary origin and the enhancement pattern reflects the vascular perfusion of the lesions. RCC metastases are usually hypervascular and consequently show intense homogeneous contrast enhancement in the arterial phase, greater than normal pancreatic parenchyma, and a tendency to pass undetected in more delayed post-contrast phases, since the difference in density between the mass and the normal pancreatic gland decreases.

In lesions larger than 1.5 cm, rim enhancement with hypodense central areas of necrosis may be seen.

Pancreatic metastases do not appear to show a predilection for a particular part of the pancreas[37,38]. Three types of metastatic involvement of the pancreas have been described in the literature. The most common type of all metastases and in particular of RCC metastases, reported in 50%-73% of cases, is that of a solitary, localized, well-defined mass. A second pattern of multiple pancreatic lesions has been reported in 5%-10% of cases, and a third pattern of diffuse metastatic infiltration causing generalized enlargement of the organ in 15%-44% of cases[9,30,39,40].

Other features described in this type of lesion are calcifications, ductal and biliary obstruction, vascular extension, and cystic degeneration, although these findings are quite non-specific.

On MRI, pancreatic lesions typically appear hypointense, compared with normal gland tissue on unenhanced T1 weighted images, both with and without fat saturation. Following intravenous contrast media injection, homogeneous enhancement is typically demonstrated in smaller lesions and rim enhancement in larger ones. On T2 weighted images, the lesions are slightly heterogeneous and moderately hyperintense. Hypointense nodules are sometimes visible on T2 weighted images, especially in the diffusely enlarged type. Diffusion weighted imaging was recently included in the standard MRI protocol; metastatic lesions typically also show a hyperintensity signal in sequences with high b-values (700-1000).

When hypervascular pancreatic lesions are depicted on contrast-enhanced CT and MRI, differentiation from a primary pancreatic endocrine tumor might be difficult. The other differential diagnoses include metastasis of hypervascular neoplasm, intrapancreatic accessory spleen and vascular lesions, such as arteriovenous fistulas or aneurysms of the splenic artery[10,19,22,32,41]. In most cases, the oncological background and existence of previous follow-up of the neoplastic disease allows a correct diagnosis, and in controversial cases a CT-guided biopsy can be performed.

Endoscopic ultrasonography

The development of imaging technology has improved the detection and differentiation of small lesions but difficulties remain. Pancreatic lesions are commonly undetected at an early stage since the symptoms of small pancreatic lesions are frequently vague and non-specific.

Endoscopic ultrasonography (EUS) is a highly sensitive diagnostic method for detection of pancreatic lesions, especially small lesions.

Pancreatic metastases appear as solid intraparenchymal space-occupying lesions with an internal structure that is much more hypoechoic than the normal pancreatic tissue, or isoechoic. These lesions are homogeneous, round, well circumscribed and associated with enhancement through transmission of the ultrasonic beam[36,42,43].

At Power Doppler or Color Doppler evaluation and with ultrasound contrast agent (CE-EUS), metastatic pancreatic tumors from renal cell carcinomas are hypervascular (hypervascular enhancement compared with the surrounding pancreatic tissue).

F-18 fluorodeoxyglucose positron emission tomography

There is no firm consensus regarding the role of this technique in pancreatic cancer and especially in metastases from RCC.

Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) has not been extensively studied for the evaluation of distant metastases from RCC. Reported studies of FDG-PET in metastatic RCC have involved few patients, and most series have compared the results of FDG-PET with clinical outcome determined by follow-up with conventional anatomic radiological techniques; moreover, pathologic confirmation of metastatic disease, if performed, was usually combined with radiological follow-up for reporting results.

In a study reported by Ramdave *et al*[44], FDG-PET identified distant metastases from RCC in six out of six patients evaluated for possible metastatic disease. Presence of metastatic disease was confirmed by pathology (fine-needle aspiration cytology) in only one of these six patients. In the same study, FDG-PET detected unsuspected metastatic disease not seen on CT in two of 17 patients evaluated for primary RCC. Metastatic disease was confirmed by biopsy at laparotomy in only one of these cases. In another study by Brouwers *et al*[45], among 20 RCC patients with 112 distant metastatic lesions evaluated by FDG scintigraphy and followed clinically, FDG-PET detected 69% (77 of 112) of the metastatic lesions. Of these, 32 lesions had not been detected by routine imaging modalities.

Table 1 Studies of renal cell cancer that include more than five patients

Ref.	Yr	*n*	5-yr survival	Median survival
Butturini *et al*[56]	1998	5	NR	24.5 mo
La Borgne *et al*[15]	2000	5	0%	35.5 mo
Kassabian *et al*[11]	2000	5	67%	Not reached
Ghavamian *et al*[59]	2000	11	81%	120 mo
Hioits *et al*[14]	2001	10	NR	4-8 yr
Faure *et al*[21]	2001	9	88%	Not reached
Law *et al*[22]	2003	14	75%	Not reached
Wente *et al*[27]	2005	15	NR	Not reached
Kohler *et al*[61]	2006	5	100%	Not reached
Crippa *et al*[10]	2006	5	80%	Not reached
Eidit *et al*[57]	2007	7	88%	Not reached
Varker *et al*[60]	2007	5	NR	Not reached
Bahra *et al*[55]	2007	9	100%	Not reached
Zerbi *et al*[12]	2008	23	88%	Not reached
Reddy *et al*[54]	2008	21	45%	58 mo
Tanis *et al*[63]	2009	10	NR	Not reached
Masetti *et al*[35]	2010	6	NR	Not reached
Konstantinidis *et al*[62]	2010	20	61%	8.7 yr

NR: Data not reported. Survival data is from the time of resection of the pancreatic metastasis, not from diagnosis of the primary tumor.

Using FDG-PET for restaging 36 patients with advanced RCC, Safaei *et al*[46] demonstrated a sensitivity and specificity of 87% and 100%, respectively.

Majhail *et al*[47] calculated the sensitivity, specificity, positive predictive value, and negative predictive value of FDG-PET for detection of distant metastases from RCC. They observed the sensitivity of FDG-PET to be 63.6%; however, in the same work the authors noted that FDG-PET was more sensitive for imaging larger lesions (sensitivity was 83.3% for lesions > 1.5 cm and 92.9% for lesions > 2.0 cm in size). Again, true-positive lesions were larger in size (mean size, 2.2 cm) compared with false-negative lesions (mean size, 1.0 cm).

Overall, FDG-PET scintigraphy is not a very sensitive imaging modality for the evaluation of metastatic RCC and may not adequately characterize small metastatic lesions. However, positive FDG-PET is predictive for the presence of RCC in imaged lesions, may complement anatomic radiological imaging modalities, and may alleviate the need for a biopsy in selected situations. A negative FDG-PET, however, does not rule out active malignancy.

PET could be used in early assessment of the response to chemotherapy, radiotherapy or both modalities. Indeed, the ability to predict therapeutic response early during a course of treatment is important since prognosis is poor, lifespan is limited and toxicity in non-responding patients is not acceptable.

OUTCOME OF SURGERY

Resection of liver, lung, and brain metastases has proven to be effective in the treatment of several types of tumors. The strongest evidence in favor of this practice exists for colorectal cancer, in which the resection of liver metastases has been shown to prolong patient survival and to improve the quality of life[16]. Moreover, study results published in the literature suggest that the resection of metastases from other types of tumors can improve patient outcome[48-50].

Although pancreatic surgery is considered one of the most technically demanding and challenging surgical disciplines, steady improvements in surgical techniques and advances in perioperative supportive care, based on a modern interdisciplinary approach that includes anesthesiology, oncology, radiology, nutritional science, and nursing, has reduced mortality to less than 5% in high-volume centers.

Standardized pancreatic resection adapted to the location of the tumor, in terms of partial pancreaticoduodenectomy, distal pancreatectomy, and total pancreatectomy, is generally recommended for the management of isolated pancreatic metastases. Because of the high recurrence rate[20], atypical local resection is confined to some exceptional cases.

Treatment recommendations for multiple pancreatic metastases vary. Whereas some advise total pancreatectomy, others[51-53] critically reject surgery on the assumption that multiple pancreatic metastases signal incipient fatal disseminated metastatic disease.

A few isolated articles describing small series of patients who underwent surgery for pancreatic metastatic disease have recently been published, reporting encouraging results[10,14,54].

We have identified 18 studies addressing pancreatic metastasectomy for RCC with five or more patients[10-12,14,15,22,27,35,54-63]. Survival results from these studies are listed in Table 1. Of the 12 studies that included long-term survival data, seven (58.3%) reported 5-year survival rates from the time of the pancreatic metastasectomy higher than 80%.

OUTCOME WITHOUT RADICAL RESECTION

In the case of unresectable disease, surgical or endoscopic palliation in association with chemotherapy can improve the quality of life but not survival, even if, in rare cases of renal cell metastases, an improved survival has been reported after palliative surgery[34,64].

In the series described by Zerbi *et al*[12], 13 patients who did not undergo resection, because of locally advanced disease or due to the presence of extrapancreatic disease, all received immunotherapy with interferon (IFN) α as first-line treatment; 6 patients underwent other therapies (interleukin-2 in 3 cases, thalidomide in 1 case, radiotherapy in 1 case, bone marrow transplantation in 1 case). The median survival was 27 mo (range 17.5 to 50.2 mo).

In this group of patients who did not undergo surgical resection, 2- and 5-year survival rates were 59% and 47%, respectively.

Table 2 Prognostic factors for risk group stratification model[70]

Factors for risk group	Poor prognostic category and factors
Factor	Category
Time from diagnosis to study entry	< 12 mo
Hemoglobin	Below lower limit of reference range
Lactate dehydrogenase	> 1.5 x upper limit of reference range
Corrected serum calcium	> 10.0 mg/dL
Previous radiotherapy	Yes
No. of metastatic sites	⩾ 2
Risk Group	No. of factors
Favorable	Zero or one
Intermediate	Two
Poor	Three or more

Patients are stratified into three groups depending on the number of poor prognostic factors found, as follows: favorable risk group, patients with zero or one poor prognostic factor; intermediate risk group, presence of two poor prognostic factors; poor risk group, presence of three or more poor prognostic factors.

PROGNOSTIC FACTORS

No prospective randomized or case-controlled studies have been performed to evaluate the role of surgical resection. In addition, many of the existing retrospective studies are limited because of the small number of patients who were treated for prolonged periods of time.

The pooled data from the 18 studies in Table 1 do not contain adequate detail to assess features for the prediction of outcome in the context of pancreatic metastasectomy for RCC. However, analyzing the three largest series reported in the literature it can be seen firstly that in their series of 21 patients who underwent pancreatic metastasectomy for RCC, Reddy *et al*[54] reported that tumor size greater than 4 cm ($P = 0.13$) and perineural invasion ($P = 0.26$) were not associated with significant differences in outcome, whereas lymph node involvement (hazard ratio 24.1, $P = 0.01$) and vascular invasion (hazard ratio 20.4, $P = 0.007$) were each associated with worse overall survival. The median survival was 4.8 years (range 0.35 to 18.3 years). Metachronous RCC had a similar survival to synchronous lesions ($P = 0.98$).

Zerbi *et al*[12] addressed the question of whether or not pancreatic metastasectomy changes the progression of RCC. They assessed a non-matched control group of patients with non-operatively managed pancreatic RCC metastasis. In this study, 13 out of 36 patients with pancreatic RCC were not offered surgery on the basis of functional status or extent of disease. These 13 patients were the control group, and their outcome was compared with outcomes for patients undergoing pancreatic metastasectomy. For the entire cohort, the median survival was 27 mo (range 0.6 to 222 mo) and 5-year survival was 47%. Patients who had tumors resected had a 5-year survival of 88% compared with 47% for the non-operative group ($P = 0.026$), suggesting a benefit of pancreatic metastasectomy.

On the other hand, in their series of 20 patients with pancreatic metastases from RCC, Konstantinidis *et al*[62] reported that, on univariate analysis, the number of metastatic nodules (solitary *vs* multiple, $P = 0.87$), the size of metastases (greater or smaller than median of 3 cm, $P = 0.78$), the location of the metastases ($P = 0.72$), 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 outcome ($P = 0.99$). Patients had median and mean follow-up of 36.8 and 38.1 mo, respectively (range 0.5 to 143 mo). 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%.

However, the treatment of pancreatic metastases from RCC remains controversial because of the relatively low frequency of this localization and the complex natural history of RCC, ranging from cases with a long disease-free interval to others with early development of widespread metastases[65].

To predict the behavior of disease in patients with metastatic RCC, several prognostic models have recently been developed[66-68]. In particular, Motzer *et al*[68,69] from Memorial Sloan-Kettering Cancer Center (MSKCC) proposed categorizing patients with metastatic RCC into one of three classes by using a model with five prognostic factors. This prognostic score was recently validated and modified by a study from the Cleveland Clinic Foundation group[70](Table 2).

CHEMOTHERAPY

Since RCC is highly resistant to chemotherapy, interleukin-2 or IFN α have been widely used as first-line treatment of metastatic disease. These agents have limited efficacy and are associated with considerable toxic effects. Response rates with these cytokines were low (5% to 20%), the median overall survival was approximately 12 mo, and the overall survival rate at 5 years was less than 10%[71-75].

Several molecularly targeted therapies have recently shown substantial clinical efficacy in patients with advanced RCC, in particular the multitargeted tyrosine kinase inhibitors (such as sunitinib and sorafenib), anti-vascular endothelial growth factor (VEGF) antibody (such as bevacizumab), and mammalian target of rapamycin (mTOR) pathway inhibitors (such as everolimus and temsirolimus). The treatment regimen is based on the MSKCC risk stratification, on the type of the tumor (clear cell renal carcinoma or not clear cell renal carcinoma), and on the previous treatment (cytokines or multitargeted therapy). Sunitinib is chosen as first-line therapy in patients with favorable or intermediate prognosis. Two phase 2 trials on sunitinib in patients treated with cytokines as first-line therapy showed that the objective response rates (as assessed by investigators and by an independent review) were 34%-40%, better than with INF α[76,77].

The subsequent randomized phase 3 trial enrolled 750 patients. There were 375 patients in the sunitinib group and 372 in the IFN group. The median progression-free survival (PFS) was 11 mo for patients in the sunitinib group and 5 mo for patients in the IFN group

Table 3 Therapeutic algorithm

Patients with clear cell renal carcinoma		First-line therapy	Second-line therapy
Without previous treatment	Prognostic grade: favorable or intermediate prognosis	Sunitinib or Bevacizumab + interferon α	IL-2 high dose or clinical trial
	Prognostic grade: poor	Temsirolimus	Sunitinib or clinical trial
With previous treatment	With cytokines	Sorafenib	Sunitinib
	With multitargeted therapy	Everolimus	Tyrosine kinase inhibitor or clinical trial
Patients with not clear cell renal carcinoma		Temsirolimus	Sunitinib or sorafenib

($P < 0.001$), with a 58% reduction in the risk of progression. Sunitinib also improved the objective response rates (47% *vs* 12%)[78]. Patients with this prognostic grade can also be treated with bevacizumab plus IFN. In the first phase 2 trials, bevacizumab improved PFS with respect to placebo (4.8 mo *vs* 2.5 mo)[79].

The AVOREN study[80], a randomized phase 3 trial, enrolled 649 patients with 327 patients on IFN plus bevacizumab and 322 patients on IFN plus placebo. Bevacizumab plus IFN showed better PFS (median 10.2 mo *vs* 5.4 mo; $P = 0.0001$) and response rate (31% *vs* 13%). The mortality risk fell by about 14%. An American phase 3 trial (CALGB 90206)[81] confirmed the good results of bevacizumab.

In patients with poor prognosis, temsirolimus is the first option. A phase 3 trial[82] compared 3 therapeutic regimens, temsirolimus *vs* IFN *vs* the combination of these 2 agents. Temsirolimus alone improved both PFS and overall survival (OS), with a reduction of the mortality risk (14%). It is also the first choice in patients with not clear cell renal carcinoma.

Sorafenib showed superiority as a second-line therapy over placebo in terms of PFS and OS in patients treated with cytokines. The TARGET study[83], a phase 3 trial, randomized 903 patients; there were 451 patients in the sorafenib group and 452 in the placebo group. The median overall survival was 19.3 mo for patients in the sorafenib group and 15.9 mo for patients in the placebo group ($P = 0.02$). PFS was also significantly prolonged with sorafenib treatment (5.5 mo *vs* 2.8 mo; $P < 0.001$), with a 49% reduction in the risk of progression. Significantly more patients in the sorafenib group than in the placebo group had partial responses or stable disease ($P < 0.001$).

In patients treated previously with multitargeted therapy, everolimus can be the first choice. A phase 3 trial compared everolimus *vs* placebo in patients treated with sorafenib and/or sunitinib. Everolimus doubled the PFS compared with placebo (4 mo *vs* 1.9 mo) and decreased the risk of recurrence.

Based on all the clinical trials, we can summarize all the evidence in a therapeutic algorithm (Table 3). In the future, personalized treatments will be prescribed according not only to clinical criteria, but also to biological and molecular factors such as for breast and colorectal cancer.

RADIOTHERAPY

Pancreatic metastases are commonly treated with surgical resection. However, such a resection cannot always be performed safely, especially in elderly patients or those with diabetes mellitus. Pancreatic metastases of RCC may be treated successfully with radiation therapy (RT).

In the literature there is only one case report of four patients[84]. These patients presented with multiple pancreatic metastases of RCC and were treated with RT combined with IFN α. Radiotherapy was delivered at 2 Gy/fraction, up to 50 Gy in 25 fractions, with three-dimensional conformal radiation therapy technique and 10 MV photon beams from linear accelerators.

In three patients, stable local disease persisted for an average time of 33.6 mo (range11 to 69 mo) after RT. In one patient, a partial response was obtained, lasting 25 mo after RT.

The European Association of Urology guidelines recommend RT for the treatment of brain and bone lesions to induce symptomatic relief of metastases from RCC. To our knowledge, there are no other previous reports of radiotherapy for pancreatic metastases of RCC.

In patients with pancreatic metastases of RCC, surgical resection with or without systemic treatment, such as cytokine therapy or antiangiogenic therapy, should be considered if complete resection is possible.

On the other hand, systemic treatment with or without RT to induce symptomatic relief and to prevent disease progression can be considered for high-risk patients, such as those with a poor performance status, diabetes mellitus, and older age.

ALTERNATIVE APPROACHES

Treatment options for unresectable pancreatic metastases of RCC are limited and new therapeutic measures should be advocated. Radiofrequency ablation (RFA) is a local ablative method that can destroy the tumor by thermal coagulation and protein denaturation. RFA has been used successfully in the treatment of unresectable solid tumors in the liver, lung, kidney, brain, breast, prostate, bone, adrenal glands and spleen[85-92]. Application of RFA to the pancreas presents potential problems related to anatomical considerations and particular properties of the pancreatic parenchyma. The risk of inadvertent thermal injury to the distal common bile duct, duodenum, transverse colon and portal vein is considerable with RFA. In addition, thermal injury to normal pancreatic tissue may cause acute necrotizing pancreatitis, pancreatic fistula or pancreatic ascites[93-101].

Elias *et al*[94] reported two cases of multiple pancreatic metastases from RCC treated by RFA. Both patients manifested acute necrotizing pancreatitis with massive destruction of normal pancreatic parenchyma.

Hadjicostas *et al*[96], based on results obtained in four patients, concluded that RFA seems to be a feasible, potentially safe and promising option in patients with advanced and non-resectable pancreatic cancer. Girelli *et al*[102], based on results obtained in 50 patients, showed that RFA of

locally advanced pancreatic cancer is feasible and relatively well tolerated, with a 24% complication rate.

Postoperative observation (clinical surveillance, laboratory tests and imaging studies) is mandatory because of the potential for major or minor, early or later complications. The most frequent complications encountered in the earlier postoperative period (within 1 wk) are fluid collection, pancreatic fistula, duodenal perforation and vascular damage. At later times, digestive or abdominal bleeding, infections or abscesses are more common. Severe acute pancreatitis is a rare complication[96]: in Girelli's[102] study, there was only one case, and none were reported in Wu's study[101]. Major complications are frequently present with RFA of pancreatic head tumors, mainly owing to the closeness of the duodenum. These lesions are more difficult to treat, as reported previously[101].

While waiting for other studies to clarify its role, RFA should be performed in high-volume centers by an experienced surgical team devoted to pancreatic surgery.

CONCLUSION

Thus, as suggested by Zerbi *et al*[12], a high index of suspicion is necessary for all patients with a history of RCC, and they should be monitored lifelong to allow the early detection of recurrence.

Because of the possibility of substantial morbidity after pancreatic resection and the questionable benefit of metastasectomy in some patients, pancreatic metastasectomy should be offered only after a thoughtful and systematic selection process. Ideally, this process would involve a multidisciplinary team that includes a medical oncologist and an experienced pancreatic surgeon. Once the decision is made to proceed with resection, evidence suggests that the procedure should be performed at a high-volume center[103,104]. In agreement with Reddy *et al*[54], we suggest the following criteria for the selection of patients for pancreatic metastasectomy: primary cancer type that is associated with successful outcome, control of the primary cancer site, isolated metastases, resectability of the metastasis, and patient fitness to tolerate pancreatectomy.

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.

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