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EDITORIAL

Pancreatic metastases: An increasing clinical entity

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Abstract

Pancreatic metastases, although uncommon, have been observed with increasing frequency recently, especially by high-volume pancreatic surgery centers. They are often asymptomatic and detected incidentally or during follow-up investigations even several years after the removal of the primary tumor. Renal cell cancer represents the most common primary tumor by far, followed by colorectal cancer, melanoma, sarcoma and lung cancer. Pancreatic metastasectomy is indicated for an isolated and resectable metastasis in a patient fit to tolerate pancreatectomy. Both standard and atypical pancreatic resection can be performed: a resection strategy providing adequate resection margins and maximal tissue preservation of the pancreas should be pursued. The effectiveness of resection for pancreatic metastases is mainly dependent on the tumor biology of the primary cancer; renal cell cancer is associated with the best outcome with a 5-year survival rate greater than 70%.

Key words: Pancreas; Pancreatic cancer; Secondary tumor; Pancreatic resection; Renal cell cancer

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INTRODUCTION

Metastatic lesions in the pancreas are rare and account for about 2% of all pancreatic malignancies[1-3]. Most patients have widespread systemic diseases at the time of diagnosis and the detection of a solitary, resectable pancreatic metastasis is uncommon. However, reports of surgically resected pancreatic metastases have recently dramatically increased and in 2008, 15 papers in the English language were published on Pub-Med indexed journals on this topic[4-18].

High-volume pancreatic surgery centers are now seeing an increasing number of patients affected by pancreatic metastases amenable to resection. Several reasons may explain this phenomenon: the introduction of standardized oncologic follow-up programs for all patients with malignant diseases; the improved sensitivity of diagnostic examinations; the better awareness of this oncological entity; the more aggressive therapeutic attitude developed by many oncologists and surgeons; and the progressive centralization of patients with surgically resectable pancreatic diseases in high-volume centers.

DIAGNOSIS

Pancreatic metastases are asymptomatic in more than 50% of cases[4,5,19]: they are often detected during follow-up investigations after surgery for a primary lesion or as an incidental finding on imaging studies performed for an unrelated indication. Symptoms, when present, are often nonspecific and subtle such as abdominal pain, weight loss or nausea; only occasionally jaundice or gastrointestinal bleeding have been reported[4,5].

When a pancreatic mass is detected by imaging, the suspicion of a metastatic disease should arise from clinical history, tumor markers assessment and computed tomography (CT) appearance. For example, metastases from renal-cell cancer (RCC) present as contrast-enhanced, hypervascular lesions[17]. A CT-guided fine-needle biopsy to confirm the clinical suspicion is seldom necessary. It is mandatory to rule out the presence of other metastatic lesions by a whole body CT and/or a PET scan.

Pancreatic metastases typically occur a long time after the removal of the primary tumor. This is particularly true for metastases from RCC where an interval of over 10 years after nephrectomy is almost the rule. In a different way, metachronous lesions from other primary malignancies tend to arise earlier although cases of solitary metastasis from colorectal cancer presenting with an interval of more than 10 years have been reported[20]. This indicates the need for long follow-up periods and a high index of suspicion to promptly detect a pancreatic metastasis.

INDICATIONS FOR SURGERY

The role of pancreatic metastasectomy is not well defined and not every pancreatic metastasis represents an indication for its removal. There is a need to balance the potential morbidity following a pancreatic resection with the oncological benefit of the removal. However, the marked decrease in mortality and major morbidity of pancreatic surgery recently observed in many high-volume centers[21] makes pancreatic metastasectomy not radically different from liver and lung metastasectomy which is now considered the standard treatment for several neoplasms. Despite the fact that the superiority of resection versus other therapeutic options has never been clearly demonstrated, surgical removal of lung and liver metastases is now routinely performed in metastatic colorectal cancer and soft-tissue sarcomas with an apparent benefit in long-term survival[22,23]. It then seems reasonable that pancreatic metastasectomy is indicated for an isolated and resectable metastasis in a patient fit to tolerate pancreatectomy. It is necessary to carefully consider the primary cancer type, its biological behavior, its outcome, the presence of synchronous or metachronous disease and the disease-free interval; however, no single cancer-type seems to be a contraindication in appropriately selected patients. It is important to evaluate each single case on an individual basis; ideally this should be done by a multidisciplinary medical team, including an experienced pancreatic surgeon and a medical oncologist. The availability and effectiveness of systemic therapies should always be considered and eventually a combined approach with pancreatic resection could be planned.

TYPE OF SURGERY

The type of surgical procedure is an important and controversial aspect in the treatment of pancreatic metastases. Some authors advocate standard radical pancreatic resection because of the risk of recurrence[24-27]. For example, Bassi, adopting a policy of atypical resections in cases of metastases from RCC, observed a 29% rate of pancreatic recurrences[24]. Other series did not confirm this finding[5]. Considering the high frequency of multiple metastases[19,28], the occurrence of a pancreatic recurrence is more likely to be the expression of an undetected multifocality than the result of an inadequate surgical procedure. The choice of a standard or an atypical surgical procedure is then probably less important than an accurate investigation for multiple pancreatic lesions. When intraoperatively facing a case of pancreatic metastasis, an attitude similar to that adopted for small endocrine tumors should be chosen: complete mobilization of the whole pancreas, careful manual palpation and intraoperative ultrasonography to search for multiple lesions. Intraoperative ultrasound plays a key role: it not only increases the accuracy in detecting all pancreatic nodules but also precisely defines the relationship between the nodule and the main pancreatic duct, allowing the most appropriate surgical procedure to be chosen. When each pancreatic metastasis is detected, the decision to perform either a standard or an atypical resection is probably not important assuming that the margins of resection are cancer-free. In fact, incomplete resection (R1 or R2) results in poor survival rates, supporting the idea that pancreatectomy should only be undertaken if complete resection is anticipated[29]. Furthermore, the main advantage of a standard resection should be an easier removal of peripancreatic lymph nodes. However, the usefulness of lymphadenectomy in this setting is actually quite controversial as several reviews reported no lymph node involvement[5,28,30] whereas in other reports a lymph node involvement was observed in about 30% of cases[4,26]. Therefore an individual surgical approach should probably be chosen with an optimal resection strategy providing adequate resection margins and maximal tissue preservation of the pancreas.

OUTCOME OF METASTASECTOMY

The effectiveness of resection for pancreatic metastasis is mainly dependent on the tumor biology of the primary cancer. According to a recent literature review[27] which included 243 patients subjected to pancreatic resection for isolated metastases to the pancreas, RCC, colorectal cancer, melanoma and sarcoma represent the primary cancer site in about 80% of all cases. In addition, data from other clinical series also indicate lung cancer as one of the most common primary malignancies metastasizing to the pancreas.

RCC is associated with the best outcome whereas lung cancer predicts the worst outcome.

Renal cell cancer

RCC represents by far the most common primary tumor in case of isolated, resectable pancreatic metastasis. In a recent review of 421 patients undergoing resection of pancreatic RCC metastases, the actuarial 5 years survival rate, calculated on 321 patients for which data were available, was 72.6% with a 5 years disease-free survival rate of

57.0%[19]. In the largest single-center experience published, an 88% 5 years survival rate was reported[5]. These figures compare favorably with those reported after lung resection of metastatic RCC where 5 years survival rates ranging from 31% to 44% are observed[31,32].

The behavior of metastatic RCC is difficult to predict and quite heterogeneous: in some cases a rapid progression of disease is observed whereas in other cases a very slow growth pattern and even spontaneous regression are reported[33]. Pancreatic metastases from RCC seem to represent a less aggressive variant of RCC recurrence although there are no studies to support such a supposition.

The contribution of surgery to the outcome of patients with pancreatic metastasis from RCC is difficult to assess. In a recent review, the survival of 321 patients undergoing surgery was compared to that of 73 non-surgically treated patients: 2 and 5 years overall survival rates were 80% and 72% in the operated group and respectively 41% and 14% in the non-operated group[19]. Similarly, in a single-center experience, 23 patients undergoing pancreatic metastasectomy were compared to 13 non-operated patients: 5 years survival rates were respectively 88% and 47%[5]. Despite the potential strong selection bias, the remarkably higher survival rate observed after surgery justifies the concept of pancreatic resection for RCC metastasis.

Single prognostic factors after pancreatic metastasectomy for RCC have not been clearly identified. From single series, tumor grade of the primary RCC[34], lymph node involvement and vascular invasion[4] have been reported as significant predictors of survival. A disease-free interval after nephrectomy less than 2 years was related to a poorer outcome in the wide review by Tanis *et al*[19]. Interestingly, neither the number of lesions nor their size showed a significant correlation with survival in any report; considering the high rate of multiple metastases currently reported (39% in the review by Sellner *et al*[28]), it is important to stress that multifocality should not represent a contraindication to surgery. Also, the previous removal of another metastatic lesion in a different organ does not represent a negative prognostic factor[5,19]: previous disease recurrence, regardless of site, should then not dissuade the surgeon from considering resection of pancreatic metastasis.

In selected cases, for example, in patients belonging to a favorable risk group (according to the Memorial Sloan-Kettering prognostic factors model[35,36]), pancreatic resection should be proposed even with another metastatic site[5].

In addition to immunoreactive cytokines, the mainstay of treatment of metastatic RCC for the last 15 years, several anti angiogenetic agents such as bevacizumab, sunitinib, sorafenib have recently showed promising results[37]. Therefore, surgical resection should not be considered the only therapeutic tool against pancreatic metastases from RCC: a combination of various treatment approaches in the different periods of the natural history of metastatic RCC might produce synergistic antitumor activity. The correct way to combine surgery with medical treatment in metastatic RCC will be an important field of investigation in the future.

Colorectal cancer

The treatment of metastatic colorectal cancer is based on a multidisciplinary approach by surgeons and medical and radiation oncologists with recent advances in the systemic therapy of this malignancy in both the adjuvant and palliative settings. Most frequently this type of disease metastasizes to the liver and lung while pancreas represents an uncommon location. Few cases of pancreatic metastasectomy for colon or rectal cancer localization are reported in the literature; a recent review by Reddy *et al*[27] collected a total of 19 reported cases, a few more derive from other single case reports[20]. However, it is well documented that resection of isolated hepatic or lung metastases from colorectal cancer in selected patients combined with effective systemic therapy results in greater survival rates[38,39]. This appears to be true despite the few data available as well as for patients undergoing pancreatectomy. In their pooled analysis, Reddy *et al*[27] found that these patients seem to benefit from surgery resulting in a 5 year survival rate approaching 30%, similar to that for hepatic metastasectomy. Moreover, it is important to stress the fundamental role that, in addition to surgery, chemotherapy and biological therapy have in the treatment of this particular disease, allowing a better long-term outcome.

Melanoma

In a different way, metastatic melanoma always correlates with a poor prognosis with modest results from systemic therapy. Both chemotherapy and biological drugs, even when combined, did not significantly improve survival rates despite carrying high toxicity. Considering patients with AJCC stage IV disease, gastrointestinal visceral metastases bear the worst prognosis[40], usually presenting at a later time; this most likely includes the rare cases of isolated pancreatic metastases. A recent review by Olilla *et al*[41] investigated the role of surgery in metastatic melanoma showing that the effectiveness of metastasectomy is dependent on the site of metastasis. Although no studies have directly addressed the prognosis and outcomes for patients undergoing pancreatic metastasectomy, the few reported data show that pancreatic resection is associated with poor outcome (pooled median survival time: 14 mo)[27]. Despite these results, as mentioned above, no other effective therapeutic weapon is available and pancreatic resection seems to be a reasonable option as long as a complete margin free resection can be achieved. Palliative surgery should only be undertaken for symptomatic patients since it is ineffective but carries the numerous risks of pancreatic surgery.

Sarcoma

In metastatic sarcomas, only gastrointestinal stromal tumors show a sustained response to systemic therapy with the recently introduced molecular targeted therapy even in unresectable disease while non-GIST systemic sarcomas are usually unresponsive to chemotherapy. In addition, reports from different groups show encouraging results from surgery in the treatment of sarcoma metastatic to lung and liver suggesting a potential role for surgery even

in the rare case of solitary pancreatic involvement[42,43]. Once again, literature data is scanty and patients undergoing pancreatic resection for isolated metastasis constitute a small sample. The reported cases, however, resulted in lower survival rates compared to results after lung or liver metastasectomy with pooled analysis showing a 5-year survival rate of 14%[27].

Lung cancer

Lung cancer metastasizes to many sites but most frequently to the bone, the liver and the adrenal glands[44] while rarely involving the pancreas. The few reports available in the literature show that small cell lung cancer (SCLC) represents the most typical histological subtype[45] metastasizing to the pancreas, usually presenting as a metachronous lesion identified at follow-up investigations. Metastatic lung cancer has a very poor prognosis, especially SCLC, and is usually treated with best supportive care or systemic therapy; nonetheless, several reports in the literature suggest that a survival benefit may be achieved by surgical treatment of solitary extracranial spread of non small cell lung cancer[46,47]. This is confirmed by a recent case report regarding a patient presenting with jaundice subsequently diagnosed with a lung adenocarcinoma with a synchronous single metastatic lesion to the pancreatic head[48]. The patient was subjected first to a pancreaticoduodenectomy and then to the removal of the pulmonary lesion; 18 mo after surgery, the patient is asymptomatic and disease-free. However, this case represents an exception since a few other reports of resected lung metastasis to the pancreatic gland resulted in frequent disease relapse and poor survival rates[27].

CONCLUSION

Pancreatic metastases represent a new clinical entity and both gastrointestinal oncologists and pancreatic surgeons should be aware of their presence. It is likely that in the near future an increasing number of patients affected by pancreatic metastases will be observed. Pancreatic metastasectomy has shown favorable outcomes so far and it should always be considered among the therapeutical options, especially in cases of RCC. A more detailed definition for the criteria for the selection of patients for pancreatic metastasectomy is needed, representing the main goal of investigations in the near future.

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