

Current status of pancreatic cancer with oligometastasis

Estado actual del cáncer de páncreas con oligometástasis

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Abstract

Background. Pancreatic cancer is the seventh leading cause of death worldwide, with ductal adenocarcinoma as the most frequent neoplasm. Half of the patients who are diagnosed have metastases at the time of diagnosis. **Objective.** A review of the treatment of resectable pancreatic adenocarcinoma with oligometastatic disease was carried out in order to present an overview of the existing evidence. **Method.** A bibliographic search was carried in PubMed/Medline, Clinical Key and Index Medicus with MESH terms, from the year 1993 to 2022. **Results.** Patients with liver or lung metastases due to pancreatic ductal adenocarcinoma who undergo surgery and chemotherapy have a longer survival in carefully selected patients. **Conclusions.** The evidence regarding surgery in patients with pancreatic ductal adenocarcinoma and oligometastasis is limited and further randomized controlled trials are needed for both scenarios. As well as established criteria that help the selection of patients who can receive this type of treatment.

Keywords: Pancreatic adenocarcinoma. Pancreatic cancer. Liver metastases. Lung metastases. Pancreatoduodenectomy. Oligometastasis.

Resumen

Antecedentes. El cáncer pancreático es la séptima causa de muerte en el mundo, siendo el adenocarcinoma ductal del páncreas la neoplasia más frecuente. La mitad de los pacientes que son diagnosticados presentan metástasis al momento del diagnóstico. **Objetivo.** Se realizó una revisión sobre el tratamiento del adenocarcinoma pancreático resecable con enfermedad oligometastásica con el fin de presentar un panorama sobre la evidencia existente. **Método.** Se realizó una búsqueda bibliográfica en PubMed/Medline, Clinical Key e Index Medicus con términos MESH desde 1993 hasta 2022. **Resultados.** Los pacientes con metástasis hepáticas o pulmonares por adenocarcinoma ductal de páncreas que son sometidos a cirugía y quimioterapia tienen una mayor sobrevida en casos cuidadosamente seleccionados. **Conclusiones.** La evidencia respecto a la cirugía en pacientes con adenocarcinoma ductal de páncreas y oligometástasis es limitada y se necesitan ensayos controlados aleatorizados adicionales para ambos escenarios, así como criterios bien establecidos que ayuden a la selección de los pacientes que pueden recibir este tipo de tratamiento.

Palabras clave: Adenocarcinoma de páncreas. Cáncer de páncreas. Metástasis hepáticas. Metástasis pulmonares. Pancreatoduodenectomía. Oligometástasis

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Introduction

Pancreatic ductal adenocarcinoma (PDA) accounts for over 85% of all pancreatic malignancies^{1,2}. The 5-year survival rate is nearly 2% to 10%³⁻⁸, with a median overall survival of < 12 months, depending on the stage⁹. It is estimated that, at the time of diagnosis, up to 50%^{6,7} of the patients already have metastases^{6,7}, being the liver the most common location, followed by the lung¹⁰.

Surgical resection is the only potentially curative treatment for pancreatic cancer¹. This study presents a systematic review of the medical literature currently available on the management of locally resectable pancreatic adenocarcinoma with oligometastatic disease with the objective of providing an overview of the existing evidence.

Method

A bibliographic search was conducted on pancreatic cancer, its distant metastases in the liver and lung, as well as the impact of surgical and non-surgical treatment on patient survival. Through PubMed/Medline, Clinical Key, and Index Medicus, with MESH terms, a search was conducted looking for studies published in English and Spanish from 1993 through 2022. Systematic review articles, epidemiological statistics, clinical practice guidelines, randomized clinical trials, meta-analyses, case-control studies, case reports, and observational studies were included. The following keywords were used: pancreatic adenocarcinoma, pancreatic cancer, liver metastases, lung metastases, pancreatoduodenectomy, pancreatic neoplasms, and oligometastases.

Results

A total of 37 articles were included: 4 randomized clinical trials, 1 clinical practice guideline, 5 meta-analyses, 3 case-control studies, 3 case reports, 2 statistical analyses, and 19 review articles. Studies selected prior to 2016 were used for historical context. A comprehensive assessment of the quality of all the studies included was conducted, and the results were synthesized through a narrative review.

Oligometastatic oncologic disease defines an intermediate state between a locally resectable tumor stage and the presence of distant metastatic disease in a single organ¹¹. It can be defined as the presence of < 5 metastases in a single organ, and all metastatic sites must be treatable safely^{12,13}.

Surgical management of hepatic metastases in other types of tumors (colorectal cancer, neuroendocrine carcinoma) has shown good 5-year survival results, achieving metastasis resection, in addition to being a safe procedure, and improving the patients' prognosis¹⁴⁻¹⁶. In recent years, new evidence on the surgical management of pancreatic cancer has shown useful results in certain patients. However, controversies still exist on the management of patients with PDA and oligometastasis.

Kandel et al.¹⁷ reported a higher survival rate and better results in a group of patients with PDA with oligometastases (to the lung or liver) treated multimodally with neoadjuvant chemotherapy, metastatic resection, or radiofrequency ablation, along with primary tumor resection, with a 2-year survival rate of 62%. Comparatively, patients with primary tumor resection without metastasis had a 2-year survival rate of 44%, while those with metastases who only received chemotherapy showed a 2-year survival rate of only 7%. Patients from the multimodal treatment group had a median overall survival of 2.7 years, compared to 0.9 years from patients with metastases treated with chemotherapy only.

There are few studies demonstrating the safety profile of resecting hepatic PDA-related metastatic lesions. The largest series reported by Hackert et al.¹⁸ included 85 patients treated with synchronous resection (72.9%), metachronous resection (22.4%) with a range of 18.4 months after primary tumor surgery, and 4 patients (4.7%) treated with hepatic metastasis resection during an initial exploration, followed by chemotherapy and primary tumor resection¹⁸. In the cases of synchronous resection, 30-day morbidity and mortality rates of 45% and 2.9%, respectively, were reported. Regarding 2-stage resection, 30-day morbidity and mortality rates of 21.7% and 4.3% were reported. After surgery, 74% of the patients received adjuvant chemotherapy. Regarding survival, it was found that after the resection of hepatic metastasis, the median survival was 12.3 months, with a 5-year survival rate of 8.1%, without significant survival differences being reported between synchronous and metachronous resections.

Similarly, Tachezy et al.¹⁹ reported on 69 patients with metastatic PDA to the liver treated with primary tumor synchronous resection and hepatic metastases who were compared with the same number of patients who only received palliative surgery without primary tumor resection. Regarding morbidity, the group of patients undergoing resection had a 68% morbidity

rate compared to the 48% rate ($p = 0.025$) of the control group. Patients with primary tumor resection and metastases had a nearly doubled survival rate compared to those from the control group (14.5 months vs 7.5 months [$p < 0.001$], and a 5-year survival rate of 5.8% vs 0%).

Zanini et al.²⁰ described the results of 15 patients with synchronous or metachronous isolated hepatic metastases of pancreatic cancer treated with hepatic resection. Ten patients were treated with pancreatoduodenectomy (67%), 3 with total pancreatectomy (20%), and 2 with left pancreatectomy (13%). One right hepatectomy, 1 bisegmentectomy, and 13 wedge resections were also performed. After resection, all patients received chemotherapy. Eleven out of these patients underwent the resection of primary tumor and synchronous hepatic metastases, while 4 patients were treated with primary tumor resection followed by metachronous hepatic metastasis resection. The median overall survival was significantly higher in patients with metachronous metastases compared to those with synchronous metastases (11.4 months vs 8.3 months; $p = 0.038$).

Dünschede et al.²¹ compared a group of patients with synchronous/metachronous resection of hepatic metastases vs neoadjuvant gemcitabine chemotherapy without surgical intervention to study survival and disease-free interval. They included 23 patients out of a group of 193 (excluding those with data on locally advanced disease and non-hepatic metastases). Of these, 14 had synchronous hepatic metastases, and 9 had metachronous hepatic metastases. Thirteen out of these 14 patients (4 with metachronous metastases and 9 with synchronous metastases) were treated with primary tumor surgical resection plus partial hepatectomy, and 10 with neoadjuvant chemotherapy. No significant differences were seen regarding the survival of patients with synchronous hepatic metastases compared to those treated with neoadjuvant therapy (8 months vs 11 months). However, in patients with metachronous hepatic metastases, the median survival since the detection of metastases increased after surgical resection compared to patients treated with chemotherapy alone (31 months vs 11 months), demonstrating that resection could offer prolonged survival and a recurrence-free interval in selected patients.

An Italian report suggested the use of neoadjuvant chemotherapy to improve survival outcomes when performing surgery in PDA with hepatic metastases. Crippa et al.²² analyzed a total of 127 patients treated with different chemotherapy regimens, observing a higher survival and fewer hepatic metastases. After

chemotherapy, restaging occurred, and according to their criteria, only 11 patients were selected for pancreatic resection after a mean 12 months since the initial diagnosis. Three of these patients were treated with synchronous resection of hepatic metastases, and the rest with pancreatoduodenectomy, along with pylorus preservation. The median overall survival was 11 months in the entire cohort (127 patients), with a median survival of 14 months in 56 patients who had partial or complete responses to chemotherapy. However, the survival of the 11 patients treated with surgery was 39 months vs 11 months in the remaining 116 patients ($p < 0.0001$).

A different study demonstrating good survival results with the use of neoadjuvant therapy also refers to restaging. In this study, Frigerio et al.²³ reported on 24 patients with hepatic metastases due to PDA treated with different regimens of neoadjuvant chemotherapy, with favorable responses. Upon restaging these patients, they were treated with surgical resection of the primary tumor and hepatic metastases. They found a median overall survival of 56 months and a median disease-free survival of 27 months since diagnosis and 13 months since surgery. These results are indicative that in patients who benefit from chemotherapy, surgical resection may lead to increased survival.

Patients with pulmonary metastases have a better overall survival compared to those with isolated hepatic or peritoneal metastases. A retrospective case-control study compared “lung-only” and “liver-only” metastases due to PDA, showing significant differences in the “lung-only” group compared to the “liver-only” group in the following parameters: female predominance (73% vs 43%; $p < 0.01$), more metachronous cases (59% vs 11%; $p < 0.0001$), fewer nodules per patient, and a lower expression of tumor markers. They reported an overall median survival of 20.8 months and 9.1 months, respectively, and a median progression-free survival of 11 months vs 3.5 months, respectively²⁴.

Better survival rates have been found in patients treated with surgical resection of pulmonary metastases compared to those treated with metastasis-directed chemotherapy or observation^{25,26}. Rare cases of solitary metastases of pancreatic cancer in the lungs can be cured with aggressive resection. However, the criteria for surgical selection still need to be elucidated.

In the study conducted by Oweira et al.²⁷, the overall survival was evaluated depending on whether surgery of the primary tumor was performed in patients with isolated hepatic, pulmonary, or distant nodal metastases. A better prognosis was seen in patients with distant nodal

or isolated pulmonary metastases compared to those with isolated hepatic metastases only ($p < 0.0001$).

Yasukawa et al.²⁸ studied 12 patients treated with resection of lung metastases due to PDA, 6 of whom received neoadjuvant chemotherapy. In 11 patients, the primary tumor was completely resected, and they received adjuvant chemotherapy. However, 1 patient received chemotherapy until complete remission. There was no recurrence in the 12 patients until the identification of lung metastases. After lung resection, the median survival was 47 months, with 3- and 5-year overall survival rates of 62.3% and 31.2%, respectively.

Discussion

Pancreatic cancer is one of the neoplasms with the highest mortality rates worldwide. Early diagnosis is challenging for doctors because it presents very non-specific symptoms, and when pancreatic tumor is suspected, it is often found at advanced stages.

In its staging, the importance of searching for metastatic lesions lies in their high prevalence and association with a worse prognosis. The National Comprehensive Cancer Network and the Spanish Society of Medical Oncology suggest performing a CAT scan on all patients and, in some cases, a positron emission tomography in patients with indicators of high risk of metastatic disease: resectable borderline disease, elevated CA 19.9 level $> 176.66^{29,30}$, large tumors, regional adenopathies, and highly symptomatic patients.³¹ It is useful to characterize the lesions, stage the disease, detect distant metastases, preoperative and pre-radiotherapy planning, and monitor metabolic response by assessing different types of treatment and possible recurrences^{29,32,33}, because it combines metabolic detection and anatomical information²⁹.

Imaging studies are of paramount importance because they facilitate the precise detection of the location and extent of the tumor, thus allowing detailed individualized treatment planning for each patient³⁴.

We should mention that 1 in 2 patients presents metastases at the time of diagnosis, and the treatment of this group is still controversial among surgeons.

Following the improvements made in locoregional and systemic therapies (neoadjuvant therapy), some patients with borderline pancreatic cancer can undergo successful resection, especially those with a functional status of 0 or 1 according to the Eastern Cooperative Oncology Group (ECOG) scale, which is associated with more chances of tumor resection without the

need for arterial vascular resections. In combination with adjuvant therapy, this results in a potentially curative treatment for patients with PDA^{35,36}.

However, the role of surgery in PDA with oligometastases has been poorly studied, and most reports are retrospective studies, which are often insufficient due to small sample sizes and limited follow-ups. Therefore, there is no conclusive evidence on its implementation.

The randomized PREOPANC³⁷ trial compared patients treated with neoadjuvant chemotherapy followed by surgery and adjuvant therapy, showing good results in the 5-year survival rate. Therefore, while surgical resection may still be controversial, it is gaining more acceptance. These types of studies set a good precedent for the implementation of randomized protocols that provide more accurate and evidence-based information.

The studies described in this work on hepatic metastases due to PDA suggest that primary tumor resection plus hepatectomy is a safe and effective procedure when performed in carefully selected patients based on the specific context of each case. Although many of the studies include patients in similar stable clinical conditions, there is no consensus on the specific variables that make a patient eligible for this type of treatment. However, they show favorable results in patients with lung metastases and metachronous metastases compared to those with hepatic and synchronous metastases.

The early detection of distant disease, local tumor resectability, with adequate staging and preoperative planning, will lead to better outcomes after surgical resection. This is further facilitated by substantial improvements in surgical techniques, pre-, peri-, and postoperative management, and chemotherapy regimens.

Conclusions

As discussed in this review, in pancreatic cancer, surgery of the primary neoplasm and metastases may be a therapeutic option and, therefore, an opportunity for long-term survival thanks to the advanced made in perioperative management. However, evidence is limited on this regard, and randomized, prospective trials with more patients are needed to establish selection criteria and treatment guidelines.

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Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

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