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Pancreatic Resections for Metastatic Disease

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<http://dx.doi.org/10.5772/intechopen.75571>

Abstract

Although the incidence of metastases to the pancreas from various primaries is very low, these lesions are usually being described as part of the systemic recurrence of different malignancies, in certain cases isolated pancreatic metastases might be encountered. When it comes to the malignancies, which might lead to the apparition of pancreatic metastases, the most common origins have been reported to be renal cell carcinoma, colon cancer, ovarian cancer and melanomas. In certain cases, patients with pancreatic metastases might be submitted to surgery with curative intent. However, it should not be omitted that pancreatic resections can be associated with higher rates of perioperative morbidity; therefore, a precise selection of the cases that are considered suitable for such procedures is mandatory. It seems that the best results in regard with long-term survival are expected in cases with isolated pancreatic metastases as well as in cases with limited extrapancreatic lesions, amenable to complete cytoreductive surgery. This chapter reviews the most important studies conducted on the theme of pancreatic resections for metastatic disease from various primaries.

Keywords: pancreatic metastases, resection, cytoreductive surgery, morbidity

1. Introduction

Pancreatic metastases from other primaries are rare eventualities, the reported incidence being less than 2% from all pancreatic lesions [1, 2]. When it comes to the most frequent tumors that might induce the apparition of pancreatic metastases, they consist of renal cell carcinomas, melanomas, breast, lung and gynecologic primaries [3]. Most times these patients are asymptomatic and are detected during the follow-up examinations with pancreatic lesions with various localizations. When symptomatic, the most commonly reported symptoms and signs

consist of vomiting, abdominal pain, jaundice, upper digestive hemorrhage or weight loss, the apparition of such symptoms being usually associated with poor prognostic.

Once the diagnostic of malignant tumor of the pancreas is established, most of the times it is very difficult to distinguish between primary malignant lesions of the pancreas and metastatic ones [4]. However, patients presenting metastatic disease are usually associated with better outcomes when compared to pancreatic primary tumors [5].

2. Imagistic studies for metastatic pancreatic lesions diagnostic

When it comes to the most efficient imagistic study in order to determine the existence of such lesions, computed tomography seems to play an important role, most commonly such lesions being diagnosed as singular, multinodular lesions or as a diffuse infiltration with hypervascular aspect [1]. However, in up to 10% of cases, metastatic lesions of the pancreas might not be seen at standard computed tomography (CT), a positron emission tomography/computed tomography (PET-CT) is being needed. In this case, a diffuse uptake revealed by PET-CT studies might be associated with benign conditions (such as Graves' disease or autoimmune thyroiditis), while focal uptake is rather significant for the presence of a malignant lesion. In such eventualities, a percutaneous biopsy is recommended in order to have a positive diagnostic of malignancy [6].

3. Therapeutic strategies in pancreatic metastases from various primaries

Unfortunately, pancreatic metastases usually develop as part of the systemic recurrence and are associated with other disseminated lesions; therefore, the patient will become a candidate for palliative oncological treatment, in order, to alleviate the symptoms. In certain cases, the pancreatic lesions will develop as oligometastatic disease and by this way, the patient will become the perfect candidate for surgical treatment with curative intent. In such cases, an important benefit in terms of survival might be obtained. However, even in cases presenting metastatic lesions, surgery has been lately implemented as standard of care due to the high morbidity rates of this kind of surgical procedures. For a long period of time, it has been considered that performing a gesture of pancreatic surgery in such cases is associated with unacceptable rate of postoperative complications including the risk of pancreatic leaks or acute pancreatitis. In the last decades, improvement in hepatobiliopancreatic techniques in association with the improvement of the postoperative care lead to a successful association of such resections as part of cytoreductive surgery for various primaries [7–10]. However, the prognostic in such cases is strongly related to the origin of the pancreatic lesion.

An interesting study conducted on the subject of pancreatic resection for metastatic disease was published by Sweeney et al. in 2009. The study had as departure point a case series of three patients with pancreatic metastases from various primaries submitted to different therapeutic

strategies; the first reported case was the one of a 51-year-old patient known with lobular breast cancer, 5 year earlier treated with lumpectomy, axillary node dissection and adjuvant hormonal therapy and renal cell cancer, submitted to left nephrectomy and adjuvant therapy consisting of interferon and thalidomide. The patient was further diagnosed with pulmonary metastases and was submitted to atypical lung resection and with an isolated pancreatic lesion measuring 4×3.1 cm at the level of the distal pancreatic tail. The pancreatic lesion was successfully resected, the histopathological studies confirming the metastatic origin from the renal cell carcinoma. However, the patient was diagnosed with disseminated liver metastases and died of disease 20 months after pancreatic surgery. The second case was the one of a 56-year-old man submitted to surgery 4 years earlier, a left pneumonectomy being performed at that moment. Four years later, he was diagnosed with an isolated lesion in the pancreatic neck, the biopsy demonstrating the metastatic origin of the lesion. He was submitted to an exploratory laparoscopy but due to the local invasion of the hepatic artery, resection was not feasible. In consequence, the patient was submitted to palliative chemotherapy and remained alive 3 years after the diagnostic of pancreatic metastases. The third case had been previously diagnosed with breast cancer for which she had been submitted to radical mastectomy followed by six cycles of chemotherapy; 5 years later, she was diagnosed with a pancreatic tumor at the junction between head and body of the pancreas, so she was submitted to a biopsy which confirmed the metastatic character of the lesion. Therefore, she was successfully submitted to surgery, an oncologic resection of the pancreatic metastasis being performed. However, the surgical procedure was followed by adjuvant chemotherapy with good long-term outcomes [11].

The authors went further and reviewed the literature regarding pancreatic metastases of various origins published until that moment. They reported a total number of 220 patients with this pathology with a median age of 59.2 years. Among cases which reported the symptomatology at the time of presentation, the authors underlined that up to 27.6% of cases were asymptomatic, among symptomatic cases the most commonly reported signs and symptoms are abdominal pain, upper digestive bleeding, weight loss and pancreatitis. When it comes to their localization, the most common pancreatic sites of metastases included pancreatic head (in 41.8% of cases) followed by body and tail (in 34.9% of cases), periaampullary region (in 8.9% of cases) and uncinate process (in 1.1% of cases); when reported, the tumor size ranged between 1 and 11.5 cm, the average size being of 3.9 ± 2.1 cm. As the originating tumors had led to the apparition of pancreatic metastases, the most common primary tumor was the kidney (in 70.5% of cases) followed by the colorectal tumors (in 6.5% of cases), melanomas (in 2.7% of cases) and malignant fibrous histiocytomas (in 1.8% of cases). Among the 220 patients initially introduced in this study, surgery was performed in only 177 cases, the other 43 patients being diagnosed with unresectable lesions. The most commonly performed surgical procedures consisted of distal pancreatectomies in 25.9% of cases and pancreatoduodenectomy in 49.7% of cases, while total pancreatectomy was needed in 18.6% of cases submitted to surgery. When it comes to the short-term outcomes, the authors underlined that the reported incidence of complications was similar to the one reported in patients submitted to pancreatic resections for pancreatic primaries and consisted most often of pancreatic fistulas (in 6.5% of cases). As for the long-term outcomes, the authors calculated the median survival as well as the 2 year and 5 year survival rates only for pancreatic metastases from renal cell carcinoma

(this subtype being the most frequently reported in the present study); therefore, among 177 patients submitted to surgery for pancreatic metastases from renal cell cancer, the median survival was 70 months, while the 2 year and 5 year overall survival rates were of 78 and 65%, respectively. These data suggest the potential benefit of pancreatic resections for metastatic lesions; it seems that the short-term outcomes are not significantly influenced by the metastatic character of the lesion, while the long-term outcomes seem to reveal significant long-term survival especially in oligometastatic lesions from renal primaries [11].

In a study conducted by Reddy et al. on 49 patients with metastatic pancreatic lesions, the main included primaries were renal cell carcinoma (in 21 cases), gallbladder cancer (in 6 cases), pulmonary cancer (in 4 cases), ovarian cancer (in 4 cases), sarcomas (in 4 cases), melanomas (in 3 cases), colorectal cancer (in 2 cases), breast cancer (in 1 case), hepatocellular carcinomas (in 1 case), seminomas (in 1 case), Langerhans cell histiocytosis (in 1 case) and nonpancreatic endocrine cancers (in one case). The study was conducted for a 38 year time period and reviewed data from 3830 patients submitted to pancreatic surgery; among these cases, the metastatic origin of the tumor was demonstrated in 1.6% of cases. The median age at the time of resection of pancreatic lesions was 60 years, while the most commonly encountered symptoms were abdominal pain (in 48% of cases), followed by jaundice (in 31% of cases). When it comes to the most commonly performed surgical procedures, they consisted of pancreatoduodenectomy in 31 cases, distal pancreatectomies in 14 cases and total pancreatectomy in 4 cases; among the 14 cases submitted to distal pancreatic resections, splenectomy was associated in 13 patients. When it comes to the short-term outcomes, the reported morbidity rates were 52% after pancreatoduodenectomy, 46% after distal pancreatectomy and 25% after total pancreatectomy; however, the overall mortality rate was 0. The most often reported complications were wound infections, followed by delayed gastric emptying or pulmonary complications. When it comes to the histopathological findings, the most often reported lymph node metastases originated from renal cell carcinomas, gallbladder carcinomas, lung, colorectal carcinomas, melanomas, seminomas, sarcomas and nonpancreatic endocrine tumors, while perineural and vascular invasion were reported in gallbladder, lung, renal cell cancers and melanomas. As for the long-term outcomes, the authors reported a median overall survival rate after pancreatic resection of 3.7 years. Among long-term survivors (defined as a longer than 10 year survival after pancreatic resection), the most commonly reported origins were renal cell carcinomas, followed by Langerhans histiocytosis and seminomas. When performing an univariate analysis, the most important prognostic factors affecting the long-term survival were represented by the presence of perineural invasion and vascular invasion; surprisingly, the diameter of the metastatic tumor or lymph node metastases did not significantly influence survival. Moreover, patients who experienced any type of surgical complication as well as male patients trended to report a poorer outcome. When it comes to the influence of the cancer type on the overall prognostic, a significant influence was reported. The poorest outcomes were reported in patients submitted to surgery for pancreatic metastases originating from melanomas, followed by cases with breast cancer. No patient diagnosed with pancreatic metastases from colorectal, lung cancer or sarcoma did experience an overall survival longer than 5 years. The best outcome was reported by the patient diagnosed with metastatic Langerhans cell histiocytosis and by the patient diagnosed with seminoma, both cases being alive more than 11 years after pancreatic surgery.

Another interesting conclusion of the study was the one regarding the time of diagnostic of the pancreatic lesions; in three cases pancreatic resection was performed synchronously with the resection of the primary tumor, the origin of the pancreatic metastases being represented by renal cell carcinoma, gallbladder cancer and ovarian cancer. In the remaining cases, pancreatic resection was performed for metachronous lesions; however, there was no difference in terms of survival between the two groups [12].

4. Pancreatic metastases from renal cell carcinoma

Renal cell carcinomas represent almost 2% of all malignant tumors in adults, being the third most common genitourinary tract cancer [13]. Although renal cell carcinoma is associated with an overall good prognostic, with 5-year survival rate of up to 95%, patients presenting distant metastases report a significant poorer outcome, with 5-year survival rates lower than 10%.

Pancreatic metastases with renal cell carcinoma origin can be diagnosed at the time of the diagnostic of the primary tumor (as synchronous lesions) or after a disease free interval (as metachronous lesions). In the second case, it seems that the prognostic is significantly influenced by the disease free survival interval, a longer period of time between the initial diagnostic and the diagnostic of metastatic lesions being associated with a lower biological aggressivity and better chances of long-term survival [14, 15]. However, it should not be omitted that pancreatic metastases from renal cell carcinoma can occur even at 10–32 years from the diagnostic of the primary tumor, so that differential diagnosis should be kept in mind any moment in which a patient known with previous history of renal cell carcinoma is diagnosed with a metachronous pancreatic tumor [16].

Patients with pancreatic metastases from renal cell carcinomas can remain asymptomatic for a long period of time or can develop signs and symptoms such as weight loss, abdominal pain, jaundice or even pancreatitis due to the Wirsung duct obstruction caused by tumor growth; in certain cases lesions located in the pancreatic head will lead to the apparition of upper gastrointestinal bleeding [17, 18].

Once a pancreatic metastasis with renal cell carcinoma origin is suspected at the imagistic studies, a fine needle biopsy might be needed in order to confirm the origin of the lesion and to decide which should be the therapeutic protocol. However, pancreatic metastases from renal cell carcinoma are the most common situation in which pancreatic resection for metastatic disease has been proposed.

When it comes to the most important prognostic factors after pancreatic resections for pancreatic metastases with renal cell carcinomas, it seems that the disease free survival plays a central role; patients diagnosed with pancreatic metastases with a disease free survival longer than 2 years seem to have an improved outcome. Other factors which seem to influence the long-term outcomes are represented by the diameter of the tumor (tumors larger than 5 cm being associated with poorer outcomes), stage at the initial diagnostic and the tumoral degree of differentiation [19, 20].

The largest series of cases submitted to pancreatic resections for metastatic renal cell carcinomas was conducted by Schwarz et al. and was published in 2014 in *Annals of Surgical Oncology* [21]. The study was conducted between May 1987 and June 2003 in 12 Franco-Belgian surgical centers and involved 62 patients submitted to surgery for pancreatic metastases from renal cell carcinomas. The median age at diagnostic was 54 years (range 31–75 years) while the most common reported symptoms were abdominal pain (in 24% of cases), anemia and gastrointestinal bleeding (in 13% of cases) and jaundice (in 10% of cases). The mean interval from the diagnostic of the primary tumor to the diagnostic of the pancreatic lesion was 9.8 years (range 0–25 years—two patients presenting with synchronous pancreatic lesions). When it comes to the most commonly performed surgical procedures, they consisted of pancreatoduodenectomy in 31% of cases, distal pancreatectomies in 40% of cases, total pancreatectomies in 23% of cases and enucleation in 6% of cases. In order to achieve negative resection margins, in six cases major vascular resections with reconstruction were performed, while *en bloc* visceral resections were needed in other four cases (consisting of colonic resections in three cases and omentectomy in one case); in other six patients the presence of other distant metastases imposed performing other visceral resections such as liver resection in three cases, contralateral adrenalectomy in three cases and contralateral nephrectomy in other two cases. The histopathological studies confirmed an unique pancreatic lesion in 39 cases, while in the other 23 cases, 2 or more metastatic lesions were described. Moreover lymph node involvement was reported in 27% of cases submitted to lymph node dissection. During the early postoperative period, the authors reported an overall mortality rate of 6.4%; after a median follow-up of 91 months, 32 patients were dead of disease, 11 cases died of other non-malignant causes and 15 patients were still alive (5 cases being alive with disease while the remaining 10 cases were alive with no signs of recurrent lesions). The authors reported a 3 year, a 5 and a 10 year survival rate of 72, 63 and 32%, respectively. Among the 37 patients who experienced recurrences, 9 cases presented pancreatic relapse, the median time to recurrence being of 44 months. Pancreatic relapsed presented as isolated metastases in five cases and as part of systemic relapse—in association with lung and liver metastases in other four patients; therefore four cases were submitted to pancreatic re-resection, the median survival time after re-resection being of 52.6 months (significantly higher compared to the one reported after conservative therapy—11.2 months, $p = 0.019$). When it comes to the most important prognostic factors influencing survival, it seems that the presence of extrapancreatic disease as well as the presence of lymph node metastases significantly decreased survival. Surprisingly, the study failed to demonstrate a significant influence of the disease free survival interval on the overall survival rate, this fact being explained by the authors by the limited number of patients introduced in the current study [21].

In a similar study conducted by Ruckert et al. and published in 2016 in the *International Journal of Surgery*, the authors reviewed data from 40 patients submitted to surgery for pancreatic metastases from renal cell carcinomas in 2 German centers between January 1993 and October 2014. These cases were submitted to surgery for pancreatic disease after a median period of 125.4 months, the most commonly performed surgical procedures consisting of pancreatoduodenectomy (in 37.5% of cases), total pancreatectomies (in 22.5% of cases), distal pancreatectomies (in 30% of cases), segmental resections (in 7.5 cases) and papillary resections (in 2.5% of cases). The most commonly encountered complication was pancreatic leak and it was

reported in 12 cases while the postoperative overall mortality was 7.5%. When it comes to the long-term outcomes, the authors reported a mean overall survival of 147.9 months; however, none of the studied factors (including body mass index, sex, time of resection, synchronous/metachronous lesions, symptomatic/asymptomatic lesions, resection status, existence of other extrapancreatic lesions, tumor dimension or lymph node status) did not significantly influenced survival. This fact was explained by the authors by the relative small number of cases introduced in the current study [22]. Another important aspect pointed out of these authors is the one regarding the lymph node status: among the 21 patients who benefited from lymph node resection 5 patients were diagnosed with lymph node metastases; therefore the authors underlined the necessity of association of lymph node dissection in such cases [22].

The outcomes after pancreatic resection for pancreatic metastases with renal cell origin are shown in **Table 1**.

| Name, year of the study | Period of the study | No. of patients | Disease free interval | Type of pancreatic resection | Early postoperative outcomes | Long-term outcomes |
|-------------------------|---------------------|-----------------|-----------------------|---|----------------------------------|---|
| Schwarz, 2014 [21] | 1987–2003 | 27 patients | 9.8 years | PD: 19 cases DP: 25 cases TP: 14 cases Enucleation: 4 cases | Postoperative mortality: 4 cases | Overall survival after pancreatic resections: 52.6 months |
| Ruckert, 2016 [22] | 1993–2014 | 40 patients | 125.4 months | PD: 15 cases DP: 12 cases Enucleation: 3 cases Broad papillary resection: 1 case | Postoperative mortality: 3 cases | Overall survival after pancreatic resections: 147.9 months |
| Markinez, 2013 [23] | 2000–2011 | 8 patients | 12.42 years | TP: 6 cases DP: 1 case Atypical resection: 1 case | Postoperative mortality: 1 case | Survival between 6 months and 95 months |
| Benhaim, 2015 [24] | 1997–2012 | 20 patients | 130 ± 59 months | PD: 6 cases DP: 5 cases TP: 3 cases Metastasectomy: 6 cases | Postoperative mortality: 1 case | Overall survival rate at 4 years: 72% |
| Zerbi, 2008 [25] | 1998–2006 | 23 patients | 8 years | PD: 4 cases DP: 11 cases TP: 2 cases Metastasectomy: 5 cases MP: 1 case | Postoperative mortality: 0 | Overall survival after pancreatic resections: 44 months |
| Yuasa, 2015 [26] | 1999–2013 | 15 patients | 13.4 years | TP: 2 cases Metastasectomy: 13 cases | Postoperative mortality: 0 | Overall survival after pancreatic resections: not reached at 3.5 year follow-up |

| Name, year of the study | Period of the study | No. of patients | Disease free interval | Type of pancreatic resection | Early postoperative outcomes | Long-term outcomes |
|-------------------------|---------------------|-----------------|-----------------------|---|------------------------------|---|
| Sohn, 2001 [27] | 1989–1999 | 10 patients | 9.8 years | PD: 7 cases DP: 2 cases TP: 1 cases | Postoperative mortality: 0 | Overall survival after pancreatic resections at 5 year follow-up: 75% |

Abbreviations: DP, distal pancreatectomy; PD, pancreatoduodenectomy; TP, total pancreatectomy; MP, middle pancreatectomy.

Table 1. Outcomes after pancreatic resections for pancreatic metastases from renal cell carcinomas.

5. Pancreatic metastases from colorectal cancer

Colorectal cancer represents one of the most common reported malignancies worldwide, being the third cause of death following breast and lung cancer and the second cause of death among non-smokers [28]. When it comes to the most common patterns of spread in colorectal cancers, they are represented by the peritoneal, lymphatic and hematogenous spread; the hematogenous route is usually related to the apparition of parenchymatous lesions located in liver, lung or brain. In certain cases, pancreatic metastases from colorectal malignancies can occur, the estimated incidence being of 2%; these types of lesions are usually associated with peritoneal carcinomatosis and less often as single lesions [29]. When it comes to the most appropriate imagistic study in order to confirm the presence of such lesions, CT has been proposed, followed by PET-CT (in cases in which although the clinical symptoms are highly suggestive for a pancreatic lesion but standard CT failed to diagnose it). It has been reported that PET-CT is a highly sensitive method of diagnostic in such cases (with an estimated sensitivity of 90–95%) while the specificity ranges between 65 and 85%; therefore performing a PET-CT in such cases seems to be responsible for the change of the therapeutic approach in up to half per cent of cases [6].

Isolated pancreatic metastases from colorectal cancer suitable for resections are scarce eventualities, only few cases being reported so far. Therefore is difficult to establish whether surgical resections of such lesions is superior to the conservative treatment such chemotherapy, due to the small number of cases submitted to surgery. However, it seems that surgery is especially useful in patients with symptomatic lesions, a satisfactory symptom relief being reported [10].

6. Pancreatic metastases from melanomas

Pancreatic metastases from melanomas are rare situations, only few such cases being presented so far; moreover, most often the cases are presented as case reports or small case series involving less than 10 cases, a standard therapeutic protocol being hard to be established. Up to half of patients presenting with pancreatic metastases from melanomas present in fact disseminated metastatic lesions in the context of the systemic recurrence, being associated

with an extremely poor prognostic. Less than 2% of patients with pancreatic metastases from melanomas will be diagnosed with oligometastatic disease, most often the primary tumor being an ocular melanoma [30, 31].

As for the long-term outcomes, patients presenting pancreatic metastases originating from melanomas with various locations seem to have a poorer prognostic when compared to other primaries due to the aggressive biological behavior of melanomas [19]. However, compared to patients treated in a conservative manner, it seems that patients submitted to surgery might benefit from a better outcome especially in cases in which complete resection of the pancreatic lesion is feasible [32, 33]. When it comes to the most important prognostic factors which might influence the long-term outcomes, it seems that a long disease free survival interval is usually associated with a lower biological aggressivity of the primary tumor, and, therefore, with a better outcome [34].

In a case series of two patients diagnosed with pancreatic metastases from melanomas at *Melbourne University, Austin Hospital, Victoria, Australia* published in 2003, the authors reported encouraging results; the first case was the one of a 45-year-old woman with personal history of ocular melanoma treated by transscleral resection 12 years earlier, the histopathological studies revealing at that moment a 10 mm mixed spindle and epithelioid cell melanoma; however, she experienced an early local recurrence 1 year postoperatively, laser therapy being performed at the time of relapse. About 11 years later (after the first local relapse), the patient was diagnosed with a pancreatic head tumor in association with three to four well defined hepatic nodules measuring 5–10 mm, while the fine needle biopsy confirmed the metastatic character of the tumor originating from the melanoma. The patient was submitted to a pylorus preserving pancreatoduodenectomy and segmental liver resection, the histopathological studies confirming the metastatic character of all the resected tumors. The patient was free of disease at 6 months follow-up. The second reported case from the same authors was the one of a 55-year-old patient known with a previous history of ocular melanoma enucleated 13 years earlier who complained of epigastric pain and was diagnosed with a tumoral mass at the level of the pancreatic head; intraoperatively multiple pigmented lesions were seen on the whole surface of the pancreas, so the patient was submitted to total pancreatectomy and remained free of disease 7 months later [34].

Wood's series conducted on a group of six patients with pancreatic metastases forming melanomas, complete surgical resection of the pancreatic lesion was associated with a median overall survival rate of 24 months, significantly higher than the survival rates after palliative chemotherapy (where the median overall survival rate does not surpass 12 months) [35, 36]. However, in Woods' study one of the most important prognostic factors was related to the resection margins, patients presenting with positive resection margins or incomplete resection being associated with a significantly poorer outcome (in fact in these cases the median survival rate was 8 months, similar to the one reported after palliative chemotherapy) [35]. In conclusion incomplete resection has no benefit in terms of survival.

7. Pancreatic metastases from breast cancer

Intra-abdominal breast cancer metastases are usually diagnosed at the level of the liver, spleen or axial skeleton [37]. When reported, pancreatic metastases from breast cancer are

usually associated with other disseminated lesions. Oligometastatic disease has been rarely diagnosed; however, these kinds of lesions might be seen after a long disease free survival interval; therefore, the diagnostic of metastatic disease should be kept in mind whenever a pancreatic tumor is diagnosed in a patient with previous history of breast cancer [38, 39]. In such cases, the clinical signs and symptoms can range from totally asymptomatic lesions to diffuse upper abdominal pain, jaundice or acute pancreatitis due to the concomitant obstruction of the common bile duct or of the Wirsung duct [38, 39].

Pancreatic metastases from breast cancer have been reported with an incidence of 13% in autopsy studies and are usually associated with other disseminated lesions, transforming the patient into a candidate for a palliative oncologic treatment [40]. However, in cases presenting as oligometastatic lesions, surgery has been proposed, this therapeutic approach being encouraged by the success reported by hepatobiliary surgeons who performed surgery for isolated hepatic metastatic with mammary origin [41].

Bednar et al. reported a case series of two patients diagnosed with pancreatic metastases from breast cancer origin. The first one was the case of a 75-year-old patient diagnosed with an invasive lobular breast carcinoma at 58 years of age for which she was submitted to a radical mastectomy at that moment, followed by adjuvant hormonal therapy based on tamoxifen. About 18 years later, the patient was investigated for weight loss, jaundice and she was diagnosed with a pancreatic head tumor; she was resubmitted to surgery, a pancreatoduodenectomy being performed. The histopathological studies confirmed the presence of a metastatic lesion originating from the primary breast cancer; postoperatively, she was resubmitted to hormonal treatment. At 4 year follow-up, the patient was alive with disease, disseminated metastatic lesions in the contralateral axilla being found. The second case was the one of a 57-year-old patient initially diagnosed with stage IIA mixed cellularity Hodgkin's lymphoma initially treated by radiotherapy, which developed 19 years after breast tumor. At that moment the patient was submitted to surgery, the histopathological studies demonstrating the presence of a high grade phyllodes tumor. About 4 years later, the patient was diagnosed with a pancreatic head tumor, in association with lung nodules which were biopsied, the histopathological studies confirming the metastatic character originating from the phyllodes tumor. Therefore the patient was submitted to palliative chemotherapy and died 15 months later [42].

8. Pancreatic metastases from ovarian cancer

Ovarian cancer remains one of the most aggressive gynecological malignancies due to the fact that most often patients are diagnosed in advanced stages of disease, when disseminated lesions are already present. In such cases, the principles of debulking surgery were successfully applied especially for pelvic confined disease. However, patients presenting extended upper abdominal lesions were considered to have a poorer outcome due to a more aggressive surgical biology. This myth was destroyed by the first studies which incorporated extended upper abdominal resections as part of debulking surgery; in Eisenhauer's study conducted between 1998 and 2003, 262 patients with advanced stage ovarian cancer

were included. These patients were divided in 3 groups according to the time when the surgical procedure was performed: there were 57 patients submitted to surgery after the date of May 2000 when extensive upper abdominal resections were performed as part of debulking surgery. Groups 2 and 3 were submitted to surgery before that date and included 122 patients submitted to cytoreductive surgery for pelvic confined disease (group 2) and 83 patients, respectively, submitted to debulking surgery for extensive lesions (group 3); therefore, most patients in the third group were suboptimally cytoreduced due to the extension of the tumoral process in the upper abdomen. The authors demonstrated a median progression free survival of 24, 23 and 11 months, respectively, for groups 1, 2 and 3. Moreover the author reported a median overall survival of 84 months for group number 2, 28 months for group number 3 and was not reached by the end of the study for group number 1. In conclusion, the authors underlined that the long-term outcomes were not influenced by the extension of the upper abdominal resections as part of debulking surgery, the only factor which strongly shortened survival being the presence of residual disease [43]. Therefore the upper abdominal resections were successfully included as part of debulking surgery for both advanced and recurrent ovarian cancer.

Pancreatic metastases from ovarian cancer usually develop as part of systemic dissemination of the malignant process, the main patterns of spread including peritoneal, hematogenous or lymphatic spread. When it comes to the pancreatic involvement due to ovarian cancer, the most commonly involved mechanisms include peritoneal and hematogenous spread.

When it comes to the association of pancreatic surgery as part of debulking surgery for advanced stage or relapsed ovarian cancer, it has been initially considered that association of such procedures will lead to the apparition of an unacceptable risk of perioperative complications. However, a study conducted by Kehoe et al. demonstrated that these surgical procedures can be successfully associated as part of debulking surgery. The authors reported a series of 17 patients submitted to distal pancreatectomies for pancreatic metastases with ovarian origin, the median age of patients being of 63 years. When it comes to the surgical outcomes, nine patients were submitted to debulking surgery to no residual disease, seven cases were submitted to optimal cytoreductive surgery while in one case a suboptimal cytoreductive surgery was performed; however, in this last case the presence of tumoral residual lesions was described at the level of the diaphragm and in the liver. When it comes to the short-term outcomes, the authors reported a morbidity rate of 24%, all patients being diagnosed with pancreatic fistulas. However, the presence of pancreatic fistulas did not impede the administration of the adjuvant therapy. Moreover, the rate of pancreatic leaks was similar to the one reported by surgeons performing pancreatic resections for pancreatic primaries, demonstrating in this way that pancreatic surgery can be safely associated as part of debulking surgery for advanced stage or recurrent ovarian cancer [44].

When it comes to the long-term outcomes after pancreatic resections for advanced stage or recurrent ovarian cancer, an interesting study was conducted in *Fundeni Clinical Hospital, Bucharest, Romania*, and was conducted by Bacalbasa et al. The study included one patient submitted to pancreatic resections as part of primary cytoreduction, four cases submitted to surgery as part of secondary cytoreduction and one case submitted to pancreatic resection

as part of tertiary cytoreduction. The patient submitted to primary cytoreduction benefitted from a distal pancreatectomy in association with splenectomy which was associated to a total hysterectomy with bilateral adnexectomy, pelvic and para-aortic lymph node dissection and parcelar gastrectomy; the long-term outcome was a favorable one, the patient being diagnosed with relapse at 54 months follow-up. Patients submitted to pancreatic resections as part of secondary cytoreduction experienced a median disease free interval of 32 months and necessitated in all cases a distal pancreatectomy. Postoperatively, two patients developed pancreatic leaks which were treated conservatively in one case and through reoperation in the second case. When it comes to the long-term outcomes, the median overall survival was 36.38 months, all cases being dead of disease at the end of the study. At the time of tertiary cytoreduction, pancreatic resection was performed in a single case, 52 months after the initial diagnostic. Although the early postoperative outcome was favorable, the patient died of disease 10 months later. The authors demonstrated in this way the effectiveness of pancreatic resections as part of cytoreductive surgery in the setting of advanced stage disease as well as for patients diagnosed with recurrent lesions [45].

| Name, year of the study | Period of the study | No. of patients | Type of pancreatic resection | Early postoperative outcomes | Long-term outcomes |
|-------------------------|---------------------|--|------------------------------|------------------------------|---|
| Chi, 2004 [47] | 2001–2002 | 70 cases, 3 patients necessitating pancreatic resections | DP: 3 cases | 0 | Not reached at the end of the study (for the entire group) |
| Eisenhauer, 2000 [43] | 2000–2003 | 57 cases, 6 patients necessitating pancreatic resections | DP: 6 cases | NR | Not reached at 36 months follow-up (for the entire group) |
| Chi, 2006 [48] | 1989–2003 | 465 cases, 2 patients necessitating pancreatic resections | DP: 2 cases | 0.6% | 106 months—in cases submitted to complete cytoreductive surgery |
| Chi, 2009 [49] | 2001–2004 | 210 cases, 9 patients necessitating pancreatic resections | DP: 9 cases | 1% | Overall survival after pancreatic resections: 54 months |
| Hoffman, 2007 [50] | 2002–2004 | 6 cases, 2 patients necessitating pancreatic resections | DP: 2 cases | 0 | Overall survival after pancreatic resections: not reported |
| Chi, 2010 [51] | 2001–2006 | 141 cases, 17 patients necessitating pancreatic resections | DP: 17 cases | 1.4% | Overall survival after pancreatic resections: 57 months |
| Rodriguez, 2013 [52] | 2001–2004 | 482 cases, 12 patients necessitating pancreatic resections | DP: 12 cases | Not reported | Overall survival after pancreatic resections: 54.6 months |
| Heitz, 2016 [53] | 2005–2010 | 578 cases, 13 patients necessitating pancreatic resections | DP: 13 cases | 2% | Overall survival after pancreatic resections: 49 months |

Abbreviations: DP, distal pancreatectomy.

Table 2. Outcomes after pancreatic resections for pancreatic metastases from ovarian carcinomas.

An interesting such case was reported by Rania Abadeer in 2010 and referred at a 43-year-old patient who was initially submitted to surgery for an adult granulosa cell tumor for which a salpingo-oophorectomy was performed. About 7 years later, the patient was diagnosed with disseminated lesions infiltrating the pelvic wall, so she was resubmitted to surgery, a total hysterectomy with left adnexectomy and bilateral pelvic lymph node dissection being performed; at that moment debulking surgery to no residual disease was achieved, the histopathological findings confirming the metastatic origin from the adult cell granulosa tumor; therefore the patient was submitted to adjuvant taxol and platinum-based chemotherapy. However, 3 years later, the patient was diagnosed with a 4.2×4.1 cm pancreatic cyst located at the cephalic level so a fine needle aspiration was performed, the cystic fluid presenting no signs of malignant cells. Due to the fact that the cyst continued experiencing a fast growth process, the patient was submitted to surgery, the frozen section of the cystic wall being suggestive for malignancy; due to this aspect, the surgical procedure was completed by performing a pancreatoduodenectomy. The immunohistochemical studies confirmed the metastatic origin of the lesion originating from the initial adult granulosa cell tumor. The long-term outcome was favorable, at 30 months follow-up the patient being free of any recurrent disease [46].

The outcomes after pancreatic resection for pancreatic metastases with ovarian cancer origin are shown in **Table 2**.

9. Pancreatic metastases from uterine body or cervix cancer

Pancreatic metastases from uterine primaries are other rare eventualities, only few cases being described so far [1, 54–56]. The main pattern of spread responsible for the apparition of pancreatic metastases with endometrial origin consists of hematogenous disseminations and it is usually responsible for the apparition of other distant lesions such as hepatic, pulmonary or splenic metastases [57]. Due to this aspect, pancreatic metastases from uterine carcinomas can be rarely treated with curative intent. The first authors who reported performing a surgical procedure for a pancreatic metastasis originating from an endometrial carcinoma came from the USA, in 1998; it was the case of a patient known with previous history of endometrial cancer who presented for upper digestive stenosis 3 years later. At this time, a 4 cm tumor located at the level of the uncinate process of the pancreas was found, so the patient was successfully submitted to surgery; unfortunately the authors did not report the performed surgical procedure or the outcome of this patient [2]. The first successful pancreatic resection for pancreatic metastases from endometrial cancer came from Dan Blazer, at *M.D. Cancer Center, Houston, Texas, United States of America*, in 2008. It was the case of a 56-year-old patient who had been previously submitted to surgery for endometrial cancer, at that moment a total hysterectomy with bilateral adnexectomy, pelvic and para-aortic lymph node dissection being performed; postoperatively, the patient was submitted to adjuvant radiotherapy. However, 31 months later, she was diagnosed with a pancreatic lesion measuring 3×3 cm in the pancreatic tail. The fine needle biopsy confirmed the metastatic origin, so the patient was resubmitted to surgery, a distal pancreatectomy being performed. The histopathological studies confirmed the metastatic origin of the lesion; however, 6 months later, the patient remained free of recurrent disease [55].

Pancreatic oligometastases with uterine cervix origin is another rare situation, a successful resection of such a lesion being reported for the first time by Wastell et al. in Westminster, London. The authors reported the case of a patient who had been initially treated by radiotherapy with curative intent for a squamous cell carcinoma; however, 5 years later, the patient was diagnosed with a pancreatic head tumor. At that moment a pancreatoduodenectomy was performed, the histopathological studies confirming the metastatic origin of this lesion; unfortunately the postoperative course was complicated by the apparition of a bronchopneumonia, the patient being dead 16 days later [58].

Another interesting case was reported by the Japanese authors in 2013 [59]. The authors reported the case of a 44-year-old patient who had been initially diagnosed with a stage IB uterine cervix cancer, the histopathological studies reporting a mixed adeno-neuroendocrine carcinoma; 8 years later, the patient was diagnosed with an isolated pancreatic tumor which was biopsied, a metastatic neuroendocrine tumor being revealed. At that moment a central pancreatectomy was performed, the histopathological studies confirming the presence of a metastatic lesion; however, only the neuroendocrine component seems to be responsible for the apparition of the recurrent disease. The long-term outcomes were favorable, the patient being free of disease at a 7 month follow-up [59].

10. Pancreatic metastases from lung cancer

Lung cancer is associated with the highest mortality rates, being associated most often with liver, brain, bone or lymph node metastases [60].

Pancreatic metastases from lung cancer are not a usual condition; in a review of 333 cases diagnosed with pancreatic metastases, the most common origin of the pancreatic lesions was represented by the renal cell carcinomas, being responsive for 45% of cases; among the remaining cases, the lung was reported as the origin of the pancreatic metastases in 14.7% of cases [61].

When it comes to the most common histopathological subtype of lung cancer which might induce the apparition of pancreatic lesions, small cell lung cancer has been most often reported; other incriminated histopathological subtypes included large cell carcinomas, squamous cell carcinomas and anaplastic bronchial carcinomas [62].

When diagnosed, pancreatic metastases from lung cancer are usually encountered as part of the systemic recurrence, with metachronous character; therefore the patient will be a candidate for palliative oncologic treatment, with low rates of long-term survival. Oligometastatic pancreatic disease with lung cancer origin appears in rare situations and it seem to be best treated through surgery with curative intent; however, the long-term outcomes failed to demonstrate good survival rates, the median overall survival ranging from a few months to a few years [10] due to biological aggressiveness of the primary tumor.

11. Pancreatic cancer from sarcomas

Metastatic lesions with sarcomatous origin are usually associated with an extremely poor outcome due to the biological aggressiveness of such primaries. When encountered, pancreatic metastases with sarcomatous origin are reported as part of the systemic disease so most often surgery is no longer a valid therapeutic option. In cases presenting oligometastatic disease, surgery might be proposed whenever the biological status of the patient will permit it. A particular problem in such cases is related to the multifocality of such lesions and to the feasibility of resection with curative intent [7].

Successful resection of pancreatic metastases from soft tissue sarcomas has been reported by the Japanese authors in two cases. The first patient had been initially diagnosed with a mesenchymal chondrosarcoma of the left thigh in 1986; 3 years later, the patient was diagnosed with isolated pancreatic lesions, the patient being submitted to surgery with curative intent; the patient remained alive for the next 10 years. The second case was initially diagnosed with a synovial sarcoma followed by pulmonary resection for metastatic disease; the case was further diagnosed with a solitary pancreatic lesion for which she was submitted to pylorus preserving pancreatoduodenectomy with good results, the patient remaining alive for more than 6 years after pancreatic resection [63].

Another extremely interesting situation was reported by another Japanese team in 2016. The authors reported the case of a 44-year-old woman who had been previously submitted to surgery for a right fibular head osteosarcoma; 3 years later, the patient was diagnosed with a metastasis in the distal pancreas, so a laparoscopic distal pancreatectomy with spleen preservation was successfully performed; the histopathological studies confirmed the metastatic origin from the initial osteosarcoma. Although the patient also reported the apparition of lung metastases, 1 year later, she was resubmitted to surgery with curative intent, the patient being still alive at the time of publishing the case [64].

A particular situation is represented by patients diagnosed with pancreatic metastases from uterine sarcomas, in cases presenting oligometastatic disease, surgery being considered as a valid option. Most often these lesions occur in patients who had been previously diagnosed with uterine leiomyosarcomas and might experience good long-term outcomes whenever a curative resection is performed [65, 66].

12. Conclusion

Isolated pancreatic metastases suitable for resection are rare eventualities; the renal cell carcinoma origin being the most frequently reported situations. When diagnosed as metachronous isolated lesions, such metastases can be submitted to surgery with curative intent, long-term survival rates being reported. Another primary with good outcomes after pancreatic resections for metastatic disease is represented by ovarian cancer, debulking surgery to no residual disease

including pancreatic resections being associated with long-term survival. When it comes to the other origins, the reported results are inconstant and no standard therapeutic protocol can be established due to the paucity of cases. However, it seems that the best outcomes should be expected in cases diagnosed with isolated metachronous lesions with long disease free survival intervals and in the absence of extrapancreatic disease. In such cases, association of surgery as part of multidisciplinary approach might improve the long-term outcomes.

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