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Pancreatic Resection for Non-Renal Pancreatic Metastases – Experience of a Single Surgical Center

Emil Matei[1,2]*, Silviu Ciurea[1], Vlad Herlea[2,3], Bogdan Mihail Dorobantu[1,2], Catalin Vasilescu[1,2]

[1]Department of General Surgery, Fundeni Clinical Institute, Bucharest, Romania
[2]Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[3]Department of Pathology, Fundeni Clinical Institute, Bucharest, Romania

***Corresponding author:**
Emil Matei, MD, PhD candidate
Department of General Surgery
Fundeni Clinical Institute, Bucharest
Romania
E-mail: emil.matei@drd.umfcd.ro

Abbreviations:
CP: central pancreatectomy;
DSP: distal splenopancreatectomy;
IHC: immunohistochemistry;
NRPM: non-renal pancreatic metastasis;
PD: pancreaticoduodenectomy:
PM: pancreatic metastasis.

Rezumat

Rezecția pancreatică pentru metastazele non-renale – experiența unui centru chirurgical

Introducere: Metastazele pancreatice sunt tumori rare reprezentând circa 2-5% din patologia malignă a pancreasului. Cele mai frecvente sunt cu origine renală, în timp ce metastazele cu alte origini (non-renale) sunt mult mai rare.
Pacienți si metodă: În centrul nostru au fost rezecați 15 pacienți cu metastaze pancreatice non-renale. Examenul anatomo-patologic imunohistochimic post-operator a demonstrat originea primitivă non-pancreatică. Pacienții au fost evaluați imagistic şi au fost diagnosticați cu boala metastatică izolată sau oligometastatică, situație care a permis rezecția pancreatică.
Rezultate: Au fost incluşi 15 pacienți cu diverse tipuri de cancer (3 - colo-rectal, 3 - căi biliare, 2 - uterin, 2 - retroperitoneal, 2 - melanoame, 2 - ovarian, 1 - feocromocitom). Cinci metastaze au fost sincrone iar 10, metacrone. Localizarea acestora a fost cefalică - 9 pacienți şi corporeo-caudală - 6. S-au practicat rezecții pancreatice standard (9 duodenopancreatectomii şi 4 splenopancreatectomii coporeo-caudale), precum şi limitate (2 pancreatectomii centrale). Postoperator au supravietuit 12 pacienți, decesul survenind în 3 cazuri. Recidiva neoplazică a fost înregistrată la 9 pacienți; la doi dintre aceştia a fost posibilă rezecția. In momentul redactării articolului, doar trei pacienți sunt în viață, fără recidivă.
Concluzii: Rezecția pancreatică pentru metastaze pancreatice non-renale este indicată în anumite cazuri selecționate, în contextul abordării oncologice multidisciplinare.

Cuvinte cheie: metastaza pancreatică, oligometastaze, rezecție pancreatică, cancer colo-rectal, cancer de căi biliare, cancer uterin, sarcom retroperitoneal, melanom, cancer ovarian, feocromocitom

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Abstract

Introduction: Pancreatic metastases are rare tumors representing about 2-5%

of pancreatic malignant conditions. The most common origin is renal cell carcinoma, while metastases with other (non-renal) origins are much rarer.
Patients and Method: Fifteen patients with non-renal pancreatic metastases were resected in our center. The post-operative immunohistochemical examination demonstrated their primary non-pancreatic origin. The patients were radiologically assessed and diagnosed with isolated metastatic or oligometastatic disease, which allowed pancreatic resection.
Results: Fifteen patients with various types of cancer (3 - colorectal, 3 - bile duct, 2 - uterine, 2 - retroperitoneal, 2 - melanomas, 2 - ovarian, 1 - pheochromocytoma) were included. Five metastases were synchronous and 10 were metachronous. Their location was cephalic – 9 patients and distal – 6. Standard pancreatic resections (9 pancreatico-duodenectomies and 4 distal splenopancreatectomies) were performed, as well as limited (2 central pancreatectomies). Twelve patients survived postoperatively; death occurred in 3 patients. Neoplastic recurrence occurred in 9 patients – resection was possible in two of them. Currently, only three patients are alive, without relapse.
Conclusions: Pancreatic resection for non-renal pancreatic metastases is indicated in certain selected cases, in the context of the multidisciplinary oncological approach.

Keywords: pancreatic metastasis, oligometastases, pancreatic resection, colorectal cancer, bile duct cancer, uterine cancer, retroperitoneal sarcoma, melanoma, ovarian cancer, pheochromocytoma

Introduction

Pancreatic metastases (PMs) are very rare tumors comprising 2 to 5% of all malignancies of the pancreas (1-4). Although, in surgical series, the most common primary malignancy responsible for PMs is renal cell carcinoma (5,6), a different range of malignant tumor can be responsible for metastasizing within the pancreatic parenchyma such as gastrointestinal malignancies, female genital tract malignancies, sarcomas, and melanoma (non-renal pancreatic metastases – NRPMs).

The role of pancreatic resection in these NRPMs is unclear because of the small number of cases and of the heterogeneity of origin. The aim of this article is to present a single center experience in NRPMs and the role of pancreatic resection.

Patients and Methods

Between January 2000 and December 2021 there were 15 patients resected for NRPMs in the Department of General Surgery from the Fundeni Clinical Institute, Bucharest, Romania, from a total number of 1976 pancreatic resections for malignancy (0.76%). PM was defined as a tumor confined to the pancreatic parenchyma without local invasion from the primary tumor, lymph nodes or local recurrence. Renal and colorectal PMs from the same center were previously published in two recent papers (6,7); the twenty patients with renal PMs were excluded from the present study.

Synchronous NRPMs were resected along with or after the primary tumor (within 6 months), with radical intent. All the patients with metachronous NRPMs underwent radical surgery for the primary tumor, followed by adjuvant therapy in eight cases.

The immunohistochemical examination of NRPMs demonstrated their origin and excluded a primary pancreatic malignancy. Data were retrospectively collected from medical records and included: age, gender, presence of symptoms, primary malignancy and treatment - surgery, adjuvant chemotherapy, previous or concomitant recurrences, the interval to development of NRPMs, site and size of NRPMs, type of pancreatectomy, postoperative course including complications or death, and recurrence and its management. The follow-up was until December 2024 or death.

Approval of the study was obtained from the Committee of Ethics of Fundeni Clinical Institute.

Results

There were 5 males and 10 females aged between 28 and 71 years old, most of the patients were between 40 and 60 years old. The patients' characteristics are reported in *Tables 1* and *2*.

The primary cancer was: colorectal (3 cases), biliary tree (3 cases), uterus (2 cases), retroperitoneal sarcomas (2 cases), melanoma (2 cases), ovary (2 cases), and one case of pheochromocytoma.

Five NRPMs were synchronous and 10 NRPMs were metachronous occurring at variable period of time between 1 and 27 years, most of them being

Table 1. NRPMs patients' general information.

Patients	15
Male/female ratio	5/10
Age range	28-71; most 40-60; mean 49
Primary tumor	
- Colo-rectal	3
- Biliary tree	3 (2 gallbladder + Klatskin's tumor)
- Uterus	2 (cervix carcinoma and leiomyosarcoma)
- Retroperitoneal sarcomas	2
- Melanoma	2
- Ovary	2
- Pheochromocytoma	1
Synchronous NRPMs	5
Metachronous NRPMs – time to diagnosis (range)	10 (1-27 ys)
Adjuvant therapy in metachronous NRPMs	8 (except one patient with melanoma and one with pheochromocytoma)
Symptoms	
- asymptomatic	9
- abdominal pain	3
- jaundice	2
- gastric outlet syndrome	1
- ascites	1
- high blood pressure	1
Site of NRPMs	
- head	9
- body-tail	6
Size (mm)	10-70
Extrapancreatic disease in metachronous NRPMs	4
- Liver	1
- Kidney	1
- Lung	1
- Peritoneal and retroperitoneal space	2
Type of pancreatic resection	
- PD	9
- DSP	4
- CP	2
Associated resection in metachronous NRPMs	4
Postoperative complications	13
Perioperative deaths	3
Recurrence	9
Time to recurrence	3-26 months
Treatment of recurrence	
- surgery	2
- systemic therapy	7
Survival period (months)	1-209

PD: pancreaticoduodenectomy; DSP: distal splenopancreatectomy; CP: central pancreatectomy.

between 1 and 5 years (*Table 2*). The 27-year recurrence occurred in a patient with pheochromocytoma, with a history of multiple resected recurrences (*Fig. 1*).

Eight patients with metachronous NRPMs underwent adjuvant therapy, according to the type of primary cancer. Nine patients were

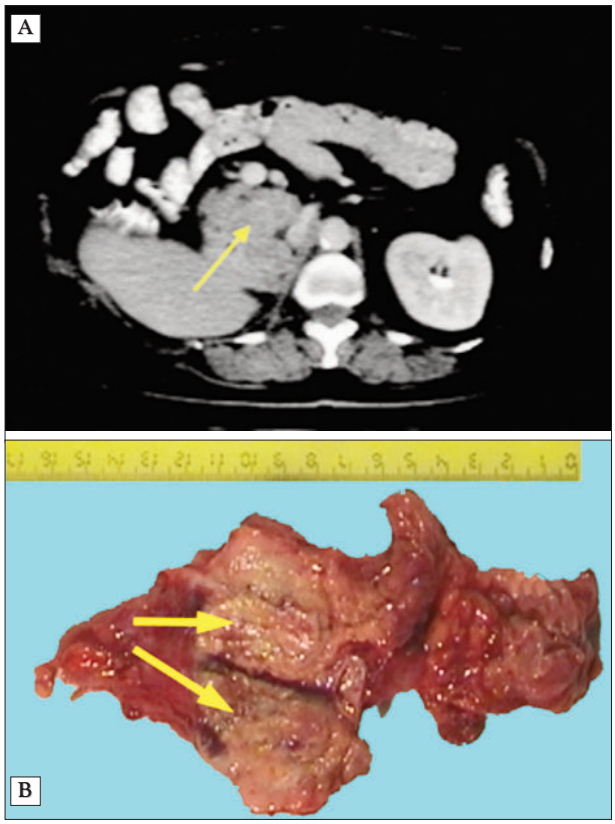

Figure 1. CT appearance **(A)** and PD resection specimen **(B)** in patient with NRPM from pheochromocytoma.

asymptomatic, their diagnosis was established during oncological follow-up; six patients were symptomatic, their main complaints being: abdominal pain (3 cases) and obstructive jaundice (2 cases).

All the patients were assessed by contrast-enhanced CT. The radiological aspect of NRPMs was variable: hypervascular (sarcomas, pheochromocytoma) or hypovascular (colorectal, ovarian) (*Fig. 2*).

MRI was performed in 4 cases and PET-CT (*Fig. 3*) in 2 patients. Endoscopic ultrasound (EUS) with biopsy was available in 1 case (melanoma).

NRPMs were located in the head of the pancreas – 9 cases, and body-tail – 6 cases. Excepting the cases of synchronous NRPMs, there were 4 patients with metachronous NRPMs and concomitant extrapancreatic oligometastatic disease in the liver, kidneys, lungs, and peritoneal/retroperitoneal space.

The patients with metachronous NRPMs were assessed by the oncological board and referred for surgical resection, without neoadjuvant chemotherapy, considering the isolated (6 cases) or

Table 2. Detailed data of NRPMs patients.

Patient		Primary tumor*			Pathological diagnosis	Interval to PMS (months)	NRPMs			Extra pancreatic resection	Dead disease	Aliveb
Sex	Age	Location	Therapy	Prior recurrence			No	Location	Size (mm)	Pancreatic			
F	47	Right adrenal	Resection	Yes	Pheochromocytoma	324‡	1	Head	40	PC	No	1	
M*	48	Gallbladder	Resection	-	Adenocarcinoma	0	1	Head	45	PC	Liver	0	
M	58	Transverse and sigmoid colon	Resection	No	Adenocarcinoma	48	1	Head	50	PC	No	1	
M	30	Common bile duct	Resection	No	Adenocarcinoma	12	1	Body-tail	40	CP	No	28	
F*	55	Gallbladder	Resection	-	Adenocarcinoma	0	1	Head	10	PC	No	59	
F	44	Right eye	Enucleation	Yes	Melanoma	48	1	Body-tail	15	CP	Lung	42	
M	28	Transverse colon	Resection	No	Adenocarcinoma	12	1	Head	70	PC	Right iliopsoatic recurrence with distal ileal invasion		209
F	29	Retroperitoneum	Resection	No	Leiomyosarcoma	24	1	Body-tail	35	DSP	Liver, right kidney	52	
F*	55	Ovary	Resection	-	Adenocarcinoma	0	1	Body-tail	10	DSP	Peritoneum, colon, spleen	158	
F*	49	Cervix	Resection	-	Carcinoma	4	1	Head	40	PC	No		176
M	60	Retroperitoneum	Resection	No	Liposarcoma	36	1	Head	40	PC	Interhepatorenal and pelvic recurrences	7	
F	44	Scalp	Resection	No	Melanoma	12	1	Head	24	PC	No	2	
F	66	Uterus	Resection	Yes	Leiomyosarcoma	60	2	Head/neck	12	PC	No	22	
F	71	Ovary	Resection	Yes	Adenocarcinoma	24	1	Body-tail	40	DSP	No		107
F*	44	Rectum	neoRT + resection	-	Adenocarcinoma	4	1	Body-tail	15	DSP	No	31	

*: synchronous NRPMs; ‡: 27 years following the primary resection (16 years after the last resected recurrence)
PD: pancreaticoduodenectomy; DSP: distal splenopancreatectomy; CP: central pancreatectomy, RT - radiotherapy.

oligo-metastatic disease (4 cases).

The resection of all NRPMs was complete, along with the extra-pancreatic disease, when present. This was achieved by using either standard pancreatic resections (9 pancreaticoduodenectomies, 4 distal splenopancreatectomies) or limited pancreatic resections (2 central pancreatectomies) (*Figs. 4* and *5*). Associated multiple visceral resections in metachronous NRPMs were performed in 4 cases with complete resection (liver, kidney, lung, and peritoneal/retroperitoneal metastases resections).

Postoperative complications were recorded in 13 patients: Clavien-Dindo grade II - 4 patients, IIIA – 4 patients, IIIB – 2 patients, V – 3 patients (*Table 3*).

There were 3 postoperative deaths secondary to septic shock of abdominal origin – acute post-operative peritonitis. The immuno-histochemistry examination of the pancreatic specimens demon-strated their non-pancreatic primary origin.

The surviving 12 patients were subsequently reassessed by the oncological team and all underwent adjuvant chemotherapy, according to the type of primary tumor.

Recurrence of the disease was recorded in 9 patients (7 metachro-nous NRPMs); only 2 patients were surgically suitable – reresec-tion (one case with three recur-rences in the remnant pancreas after central pancreatectomy), the rest being treated by systemic therapy (*Table 4*). With the excep-tion of one patient, 8 patients died of recurrence. Out of the 3 patients without recurrence, one died of unrelated cause.

The survival period was variable between: 1-209 months – 3 patients being currently alive, without recurrence.

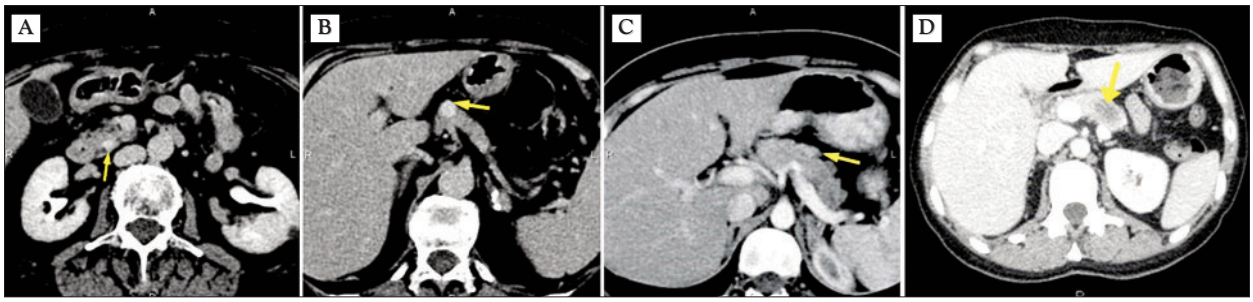

Figure 2. CT appearance of hypervascular (**A, B** – uterine leiomyosarcoma, **C** – retroperitoneal sarcoma) and hypovascular (**D** – colorectal cancer) NRPMs.

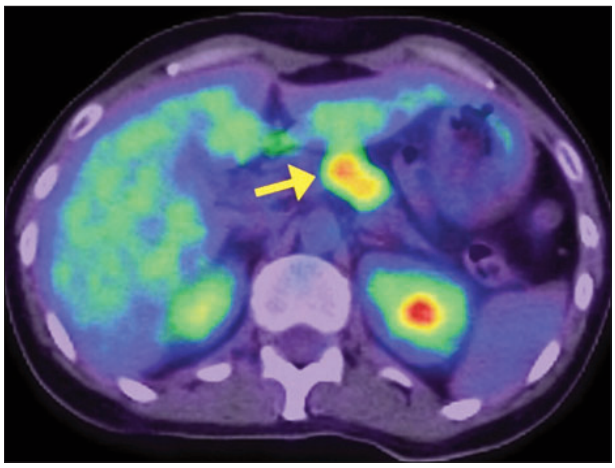

Figure 3. PET-CT appearance of colorectal NRPM.

Table 3. Postoperative complications of NRPMs patients.

Type of complication	Number of patients	Treatment
Acute postoperative peritonitis	3	Surgery
Postoperative peritoneal bleeding	1	Surgery
Splenic Infarction	1	Splenectomy
Postoperative abdominal abscess	2	Percutaneous drainage
Pancreatic fistula	3	Conservative management
Upper gastrointestinal bleeding	2	Endoscopic hemostasis
Acute coronary syndrome	1	Pharmacological treatment

Discussion

PMs are rare (2-4), most of them originating from renal cell carcinoma – 50-70% (6,8). Non-renal PMs are extremely rare, with heterogenous primary cancer origin: gastrointestinal tract (colon, rectum, stomach, liver, gallbladder, esophagus), lung, female genital tract (breast, ovary, uterus), thyroid, testicle, melanoma, and retroperitoneal sarcomas (1). The frequency of the NRPMs is different in surgical and autopsy series depending on the aggressivity of the primary tumor and extension of disease (1). In our experience there were 15 NRPMs vs. 20 renal carcinoma metastases (43%).

The way of spreading is variable and depends on the primary. It is hematogenous in most cases, considering the rich blood supply originating in the celiac axis and superior mesenteric artery (colorectal cancer, lung cancer, breast cancer, sarcomas, melanoma); other possible seeding ways are

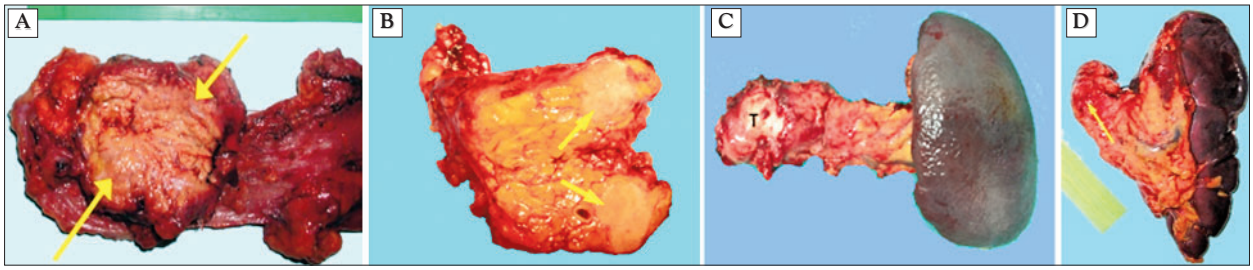

Figure 4. Standard pancreatic resection specimens: PD for gallbladder carcinoma **(A)** and uterine leiomyosarcoma **(B)** PMs; DSP for colorectal carcinoma **(C)** and retroperitoneal sarcoma **(D)** PMs.

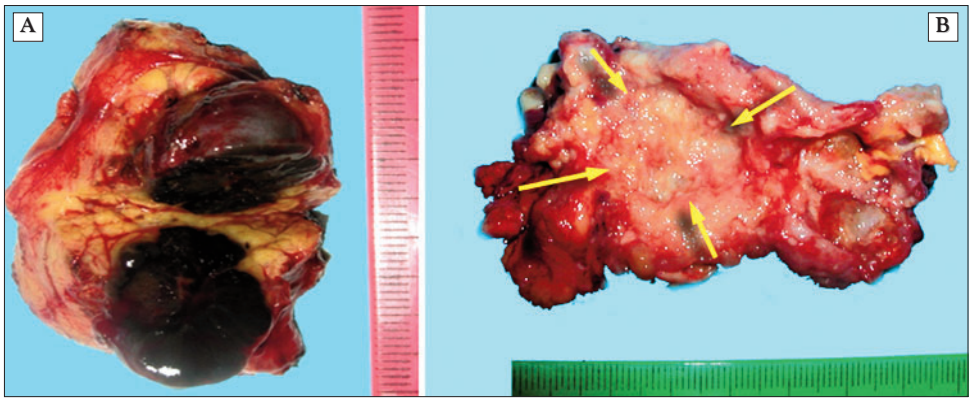

Figure 5. Limited pancreatic resection specimens – central pancreatectomy in melanoma **(A)** and Klatskin's tumor **(B)** PMs.

lymphatic (gastric cancer, esophageal cancer, cervix carcinoma, ovarian cancer) or peritoneal (ovarian cancer, cervix carcinoma). "Seed and soil" hypothesis can explain the development of PMs (9) by the nesting of circulating tumoral cells in the pancreas, where the environment may favor the tumoral growth.

The time of development of NRPMs is variable, but generally shorter than in renal PMs and associated with poorer prognosis (10). In this series there were 5 synchronous NRPMs; most of the metachronous NRPMs developed between one and five years after resection of the primary. The development of a pheochromocytoma PM 27 years following the primary resection (16 years after the last resected recurrence) is worth mentioning.

NRPMs tend to be multivisceral, while renal PMs tend to be isolated (10). From all 10 metachronous NRPMs, 4 were multivisceral.

In the presence of close oncological follow-up these patients are most likely asymptomatic. Symptoms are present in large NRPMs, depending on the site of metastasis and consist of abdominal pain, obstructive jaundice, acute pancreatitis and are associated with advanced disease with poor prognosis. In this series 6 patients were symptomatic having abdominal pain as the main complaint. It is worth noting the reappearance of high blood pressure in the patient with recurrent pheochromocytoma.

Increased serum tumoral markers correlate with tumor burden, presence of metastases and poor prognosis. CEA, CA19.9, CA 125, CA15.3, alone or in combination panels can be useful tools in diagnosis of NRPMs. New emerging biomarkers such as circulating tumor DNA, non-coding RNA, circulating RNA, gut microbiota may offer new insights, may improve the NRPMs diagnosis and tailor the oncological decision. In the metachronous series of NRPMs only one patient had increased

Table 4. Recurrence after NRPMs resection and management (S – synchronous, M – metachronous)

Patient		Synch/meta NRPMs	NRPMs size	Multivisceral disease	Time of recurrence (months)	Location of recurrence	Treatment
M	30	M	40	no	26	massive celiac	Systemic
F	55	S	10	pancreas	47	liver	Systemic
F	44	M	15	lung	30	pancreas – head (1) and tail (2); peritoneal – mesosigmoid; right buttock fat	Surgical
M	28	M	70	right iliopsoatic recurrence with distal ileal invasion	19	peritoneal – mesentery	Surgical
F	29	M	35	liver and right kidney	28	lung	Systemic
M	60	M	40	Interhepatorenal and pelvic recurrences	5	lung	Systemic
F	44	M	24	no	1	multivisceral	Systemic
F	66	M	12	no	3	liver	Systemic
F	44	S	15	no	4	lung	Systemic

tumoral markers (CEA, CA 19.9) after colorectal carcinoma.

Imaging work-up is complex considering stage IV neoplasia and consists of ultrasound, contrast-enhanced computed tomography, and MRI. Based only on this aspect it is difficult to differentiate these NRPMs from primary malignancy of the pancreas. PET-CT is compulsory in most cases in order to detect other possible metastatic sites with subsequent oncological decision. EUS is also essential by allowing biopsy with histological diagnosis.

Imagistically and histologically, these tumors can present in various forms: solitary (78.8%), multiple (16.7%), or diffuse (4.5%)(11).

Immunohistochemistry is the mainstay of final diagnosis and also of paramount importance for oncological decision.

Differential diagnosis should be done with primary exocrine malignancy (GI malignancies, breast cancer), primary endocrine malignancy (sarcomas, hepatocellular carcinoma, Merkel cell carcinoma) and primary serous adenocarcinoma of the pancreas (ovarian carcinoma). The presence of previous personal malignancy should raise the suspicion of NRPMs.

The oncological assessment is mandatory considering stage IV malignancy and able to dictate the status of disease and type of therapy: systemic therapy, surgery, chemotherapy, radiotherapy, or local ablation.

For oligometastatic disease or isolated PMs, most protocols favor surgical approach (12,13). Extensive metastatic disease including the pancreas requires systemic treatment; palliative surgery may be considered in some cases. The type of pancreatic resection is debatable, both standard and limited are accepted with for and against arguments, as long as complete resection is obtained (14-16). Most pancreatic resections from this series were standard - 13 vs. only 2 limited resections. Multivisceral resections can be performed in oligometastatic disease in order to achieve a R0 resection, but with increased morbidity and mortality.

Oncological reassessment is mandatory, as long as recurrence is frequent, with subsequent adjuvant therapy specific to the primary tumor.

The recurrence is frequent and associated with aggressivity of the primary disease, size of NRPMs and extrapancreatic disease. In this series 9 out of 12 patients developed recurrence.

In case of recurrence, the surgical approach is less possible, most patients being referred for systemic therapy. In this series, two patients (one with multiple sites of recurrence of malignant melanoma at over two years following a central pancreatic resection, and another one with peritoneal recurrence), underwent complete resection. Both of them were referred to the oncologist for systemic therapy after surgery.

Colorectal PMs appear late in the evolution of colorectal carcinoma, are rarely isolated and synchronous, most cases having multiple organ metastases and being referred to systemic therapy (17). For those with isolated or oligometastatic disease, pancreatic resection can be indicated along with systemic therapy (7). Sperti et al. considered pancreatic resection as palliative treatment (18).

Gallbladder carcinoma, an aggressive malignancy of the gastro-intestinal tract, is usually associated with retroduodenopancreatic lymph node involvement, thus a pancreaticoduodenectomy is required. NRPMs are rare, often found incidentally on the PD specimen (19;20), as in our two cases. Reddy at al. considered that multiorgan resection can be associated with increased survival, but this can be biased by the small number and selection of the patients (21).

Hilar cholangiocarcinoma - Klatskin's tumor can metastasize in the pancreas. To our knowledge this is the first case reported in the literature; interestingly, the PM was located in the body of the pancreas, instead of the head, which is anatomically and lymphatically connected to the biliary tree.

Female genital tract tumors (uterus, ovary) are rarely associated with PMs. In ovarian cancer, involvement of the pancreas is usually secondary by direct peritoneal invasion, which is not considered PM. True PMs from ovarian cancer probably occur by hematogenous or lymphatic way (22-25). Most of ovarian PMs have cystic features and can be misdiagnosed for primary cystic pancreatic neoplasia, EUS-FNA is important for diagnosis (24). Cervix carcinoma can rarely lead to NRPMs, requiring differential diagnosis with squamous primary pancreatic carcinoma (26,27). NRPMs from uterine leiomyosarcoma are rare - some of them can be preceded by extrapancreatic metastases (lungs); the case from this series was previously published (28).

Recurrences of retroperitoneal sarcomas (liposarcomas, leiomyosarcomas) are frequent, happening locally (retroperitoneal space and organs) or at distance (lungs, liver). Involvement of the pancreas is rare, usually multivisceral, requiring complex surgery as in our two cases (liver, kidney) (29-31). Complete resection of the

recurrence is the key of local control of this malignancy. Lee at al. reported in 2020 the largest series of PMs from sarcomas to date – 12 cases; metastatic sarcoma comprised 10% of all PMs and he concluded that surgical resection has the potential for increased survival (29).

Metastatic melanoma is treated by immunotherapy, targeted therapy, surgery, and radiotherapy (32). Surgical approach along with stereotactic radiation, and talimogene laherparepvec oncolytic viral therapy is recommended in patients with oligometastatic disease as long as complete curative resection is achieved (33-36). Reddy et al. concluded that patients with NRPMs from melanoma have the worst prognosis (21). Gamboa et al. considered that surgery may play a larger role as "consolidative" therapy (37). One of our two cases of melanoma, with multicentric metastases (pancreas and lung) required sequential surgical resections and was previously published (38).

Metastatic pheochromocytoma is rare and only 15-20 % of tumors are malignant, as reported by Jasim et al. (39). It can be responsible for infrequent metastases in breasts, ovaries, pancreas, brain, and skin. In these patients, the authors recommend close observation or treatment by antiresorptive medications, surgery, and/or ablative procedures correlated with the behavior of the metastatic disease. For patients with symptomatic oligometastatic secondary to pheochromocytoma (germline succinate dehydrogenase subunit D gene pathogenic variants), a clinical guideline recommends local therapies (e.g., surgery, therapeutic radiation, interventional radiology procedures) (40).

Lung cancer NRPMs are the most common finding in autopsy series, as reported by Adsay et al. (1), but are usually associated with extensive disease and not suitable for surgery.

The prognosis of NRPMs is related to the primary and extension of the disease. Synchronous NRPMs have a worse prognosis than metachronous NRPMs, related to aggressivity and extension of the primary tumor and complexity of surgery.

This study is limited by a few drawbacks: retrospective study, few cases over a long period of time, different origins, unclear way of metastasis to the pancreas.

Conclusion

The possibility of NRPMs should be considered in any patient with a pancreatic mass and a history of malignancy. An extensive imaging and histological work-up should be performed preoperatively in order to differentiate NRPMs from primary malignancy of the pancreas. The management of these patients should be multidisciplinary and a close follow-up can increase the rate of early diagnosis. Surgery can be an important tool in the oligometastatic or isolated disease and should be tailored for each patient.

Conflicts of Interests

The authors declared no potential conflicts of interest.

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