

REVIEW ARTICLE

Pancreatic metastases: An updated narrative review of epidemiology, diagnosis and management illustrated by a rare case of pulmonary artery intimal sarcoma

Fátima Carrasco-Valero¹, Indra D. Sanoja-Fernández¹, Sara Custodio-Cabello^{2,3}, José Ramón Sevilla-Resúa¹, Sheherezade Gallego-Nieto¹, Maria Carmen Montero-Hernández^{1,3}, Beatriz Chacón-Ovejero⁴, and Luis Cabezón-Gutiérrez^{2,3*}

¹Internal Medicine Department, Torrejón University Hospital, Torrejón de Ardoz, Comunidad de Madrid, Spain

²Medical Oncology Department, Torrejón University Hospital, Torrejón de Ardoz, Comunidad de Madrid, Spain

³Facultad de Medicina, Francisco de Vitoria University, Pozuelo de Alarcón, Comunidad de Madrid, Spain

⁴Department of Pharmacy and Nutrition, Faculty of Biomedical and Health Sciences, Universidad Europea de Madrid, Villaviciosa de Odon, Madrid, Spain

***Corresponding author:**
Luis Cabezón-Gutiérrez
(lcabezon@torrejonsalud.com)

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Abstract

Background: Pancreatic metastases (PM) account for 2%–5% of pancreatic neoplasms diagnosed clinically, while autopsy series report a 3%–12% prevalence, reaching 43% in advanced malignancy. This statistic suggests underdiagnosis of silent lesions mimicking primary pancreatic tumors, representing a major diagnostic challenge. **Aim:** This study aims to summarize evidence on PM etiology, diagnosis, and management, as illustrated by an exceptional case of acute pancreatitis (AP) secondary to pulmonary artery intimal sarcoma (PAIS). **Methods:** A narrative review of the medical literature was conducted in June 2026 using PubMed/MEDLINE. Publications available up to January 2026 were reviewed, including electronic ahead-of-print publications. Relevant original studies, systematic reviews, pooled analyses, and clinical guidelines were reviewed, synthesized, and integrated with the case. **Results:** Renal cell carcinoma (RCC), which accounts for 30%–70% of reported PM in clinical and surgical series, is characterized by indolent biology and latency periods exceeding ten years. Sarcomas, which represent 4.3%–7.2% of reported PM, are biologically aggressive sources of PM. AP presentation is exceptionally uncommon and is a result of mechanical pancreatic duct obstruction. Endoscopic ultrasound-guided fine-needle biopsy is considered the diagnostic standard, with a 97.9% accuracy. Metastasectomy achieves a 76.6% five-year survival rate in RCC cases. In PAIS cases, AP has been reported to resolve following systemic chemotherapy; however, this temporal association should not be interpreted as evidence confirming the proposed pathogenic mechanism. **Conclusion:** PM should be considered in any pancreatic mass or AP of uncertain origin in patients with cancer. The oligometastatic disease model (≤ 5 lesions) supports curative-intent or prolonged systemic disease-control strategies. **Relevance for patients:** Accurate diagnosis prevents staging

errors, preserves pancreatic function, and supports prolonged radiological surveillance in tumors with pancreatic tropism.

Keywords: Pancreatic metastases; Secondary pancreatic tumors; Acute pancreatitis; Oligometastatic disease; Pulmonary artery intimal sarcoma

1. Introduction

The pancreas has historically been considered relatively resistant to metastatic involvement; however, contemporary evidence has challenged this perception. Pancreatic metastases (PM) are an uncommon clinical entity, accounting for only 2%–5% of all malignant pancreatic neoplasms identified in clinical practice.^{1–4} However, this statistic is markedly contradicted by autopsy findings. Autopsy series report a 3%–12% prevalence of PM in patients with systemic malignancy, reaching up to 43% in specific series of patients with advanced disease. These findings suggest that a considerable proportion of PM either remain clinically silent and underdiagnosed or are mistakenly attributed to generalized systemic disease progression without precise local identification.^{4–6} Their ability to mimic primary pancreatic tumors represents a major diagnostic and therapeutic challenge.^{1,7}

The clinical relevance of PM lies not only in their rarity but also in their remarkable biological and radiological mimicry.^{1,7} Up to one-third of these lesions are initially misdiagnosed as primary pancreatic tumors, particularly pancreatic ductal adenocarcinoma (PDAC), which accounts for more than 90% of solid pancreatic masses.^{1,8,9} It is essential to correctly distinguish primary PDAC from PM, as the tumor biology of these entities differs profoundly, resulting in markedly different therapeutic strategies and prognoses.^{1,2} While patients with primary PDAC have 5-year survival rates of below 10%, patients with certain metastatic lesions, particularly those of renal origin, are able to achieve 5-year survival rates exceeding 75% following successful surgical resection.^{8,10,11}

From a clinical perspective, presentation is equally challenging. Approximately 40%–70% of patients with PM remain asymptomatic at diagnosis, with lesions detected incidentally during surveillance following the diagnosis of a primary malignancy.^{7,10,12} When symptoms occur, they are usually nonspecific, including dull abdominal pain (34%–45%), obstructive jaundice (20%), and weight loss.^{4,10,12} In rare cases, however, PM may present as acute pancreatitis (AP).¹² This complication is generally attributed to mechanical obstruction of the main pancreatic duct caused by tumor infiltration or extrinsic compression, and

has only been reported anecdotally, mainly in association with lung and breast malignancies.¹²

This review is justified by the need for a critical synthesis of the available evidence in an era of major technological advances. The widespread implementation of endoscopic ultrasound-guided fine-needle biopsy (EUS-FNB) has achieved diagnostic accuracy exceeding 97%, substantially improving diagnostic accuracy and facilitating clinical decision-making.^{4,7} Furthermore, the emergence of the oligometastatic disease paradigm has prompted reconsideration of therapeutic aggressiveness.^{13,14} The clinical case presented in this review—a patient with pulmonary artery intimal sarcoma (PAIS) and presumed PM presenting with AP—illustrates this unusual scenario. PAIS is a highly malignant vascular tumor that frequently mimics chronic pulmonary thromboembolism (PTE), adding further diagnostic complexity and highlighting the importance of this review in guiding patient selection and emphasizing the need for lifelong radiological surveillance.^{1,2,15}

2. Illustrative clinical case

While undergoing the etiological work-up of a thromboembolic event, a right parahilar mass was identified in a 51-year-old man with a 75-pack-year smoking history and a previous episode of PTE. When he was admitted to the Internal Medicine Department, Torrejón University Hospital, for evaluation, he was suffering from constitutional symptoms and dyspnea. During hospitalization, he developed anorexia and sudden-onset severe epigastric pain that was refractory to analgesic therapy. Physical examination revealed localized superficial epigastric tenderness.

Based on the characteristics of the abdominal pain and the patient's medical history, the differential diagnosis included AP and biliary disease. Laboratory tests showed elevated levels of serum amylase (252 U/L), lipase (759 U/L), and high-sensitivity C-reactive protein (28.82 mg/dL).

Computed tomography (CT) revealed solid pulmonary lesions, mediastinal infiltration, tumor thrombosis involving the right main pulmonary artery and the

ipsilateral superior lobar vein, massive right pleural effusion, and multiple pancreatic lesions suggestive of metastatic disease. Subsequent fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) showed increased pathological FDG uptake in both the pulmonary and pancreatic lesions. Core needle biopsy of the right middle-lobe pulmonary lesion confirmed the diagnosis of PAIS with metastatic disease.

Based on these findings, systemic chemotherapy was initiated. Following treatment, the patient's epigastric pain resolved, accompanied by normalization of serum lipase levels.

3. Methods

This narrative review was designed to provide a contemporary overview of the epidemiology, pathophysiology, diagnosis, management, and prognosis of PM by integrating current evidence with an illustrative clinical case of PAIS presenting as AP.

A literature search was performed in June 2026 using PubMed/MEDLINE. Eligible studies included publications available up to January 2026, as well as articles published online ahead of print. The search strategy combined Medical Subject Headings (MeSH) and free-text terms, including "Pancreatic Neoplasms/secondary," "Pancreatic metastases," "Secondary pancreatic tumors," and "Intimal sarcoma."

Guidelines and consensus documents, where relevant to pancreatic neoplasms or metastatic disease, were also reviewed. Additional references were identified through manual screening of the bibliographies of relevant articles.

Priority was given to systematic reviews, pooled analyses, multicenter studies, clinical practice guidelines, and high-quality observational studies. Because of the rarity of PM developing from PAIS, selected case reports and small case series were also included if they provided clinically relevant information.

The available evidence was critically synthesized to summarize current knowledge, identify areas of consensus and uncertainty, and discuss their clinical implications in the context of the presented case. Owing to the narrative nature of this review, a formal systematic review protocol or quantitative meta-analysis was not performed.

4. Origin and pathophysiology of pancreatic metastases

Pancreatic colonization by distant tumor cells is not a random event but rather the result of specific biological patterns and metastatic pathways that have been extensively investigated over the past decades.²

4.1. Renal cell carcinoma: The predominant primary tumor

Across published studies of PM, renal cell carcinoma (RCC), particularly the clear cell subtype, is the most common primary tumor, accounting for 30%–70% of reported PM cases.^{2,5,10,12} These proportions should be interpreted in the context of the heterogeneity of the published evidence, including differences in study populations and designs.

This predominance is sufficiently pronounced that RCC is considered the biological paradigm of PM.² These lesions are typically metachronous and show a uniform distribution throughout the pancreatic head, body, and tail, occurring with similar frequency irrespective of the side of the primary renal tumor.^{4,5,12} Other solid tumors account for smaller proportions of reported PM, which include, in decreasing frequency, lung cancer (3.1%–21%), colorectal cancer (8.8%–14%), melanoma (7%–9.1%), and breast cancer (4.3%–8%).^{7,10,12,16} More recently, advances in molecular characterization and machine learning-assisted biomarker discovery have highlighted the growing importance of defining tumor-specific biological signatures to refine precision oncology strategies.¹⁷ In line with this evolving paradigm, PM developing from RCC has emerged as a distinct biological entity, exhibiting recurrent *PBRM1* alterations, enhanced angiogenic signaling, and a relatively immune-quiescent microenvironment, which are features that may underlie their indolent clinical behavior and distinct therapeutic implications.¹⁴

4.2. Sarcomas: The rarity and aggressiveness of the presented case

Sarcomas are an uncommon source of pancreatic metastatic disease, accounting for 4.3%–7.2% of reported PM.^{7,10,12,16} Among them, PAIS represents an exceptionally rare biological entity. Unlike the indolent course of RCC, intimal sarcoma is characterized by highly aggressive tumor biology and rapid systemic hematogenous dissemination, which often present synchronously.^{10,12,15} The patient described in this review exemplifies this aggressive behavior, as multiple pancreatic lesions were identified synchronously during the evaluation of an active pulmonary vascular disease, contrasting with the prolonged latency typically observed in other malignancies.¹²

4.3. Metastatic pathways and the "seed and soil" hypothesis

The selective tropism of RCC for the pancreas is explained by the "seed and soil" hypothesis, which proposes that metastatic colonization depends on the interaction between the intrinsic properties of tumor cells (the "seed") and the specific microenvironment of the pancreatic

parenchyma (the “soil”).^{2,14} Given that renal PM are frequently multifocal and show no anatomical predilection within the pancreas, systemic hematogenous spread through the pancreatic arterial circulation is considered the predominant metastatic route, rather than lymphatic dissemination or local venous extension.^{2,5,12}

In vascular tumors such as intimal sarcoma, dissemination also occurs through the bloodstream, but it is accompanied by a much more destructive pattern of local invasion. The present case highlights a distinctive pathophysiological mechanism whereby pancreatic metastasis caused AP through mechanical obstruction of the pancreatic duct secondary to tumor infiltration or extrinsic compression.^{12,18} This presentation is rarely described in the literature on secondary pancreatic tumors. Therefore, the present case underscores the capacity of certain sarcomas to acutely disrupt pancreatic ductal anatomy.¹²

4.4. Tumor dormancy and latency interval

One of the most distinctive features of PM is their ability to develop after exceptionally long latency periods, a phenomenon attributed to tumor dormancy.^{1,2} RCC exemplifies this feature, with a median disease-free interval (DFI) of 7–10 years after nephrectomy and documented cases of PM occurring as late as 27 and 32 years following the diagnosis of the primary tumor.^{1,2,5,12} By contrast, lung and colorectal cancers typically exhibit much shorter latency periods, often less than two years, and may also present synchronously.^{10,12} Understanding these latency patterns is essential for patient follow-up. Although the risk of recurrence declines after five years in most malignancies, lifelong surveillance should be considered in patients with tumors exhibiting pancreatic tropism.^{2,10}

5. Clinical presentation and diagnosis

The diagnosis of PM remains one of the greatest challenges in pancreatobiliary oncology because of their low incidence and their remarkable ability to clinically and radiologically mimic primary pancreatic tumors.

5.1. Clinical presentation

Approximately 40%–70% of patients with PM are asymptomatic at the time of detection.^{10,12} In these cases, the lesions are incidental findings identified during radiological surveillance of a previously diagnosed malignancy using CT or magnetic resonance imaging (MRI).^{2,7} When patients become symptomatic, clinical manifestations generally result from mass effect or infiltration of adjacent structures and are usually nonspecific. Abdominal or back pain is the predominant symptom (34%–45%), followed by obstructive jaundice (20%–21%), nausea, weight loss, and, less frequently, upper gastrointestinal bleeding.^{4,7,10,12}

Acute pancreatitis represents an exceptionally rare mode of presentation, having been reported only anecdotally in the literature, and is most commonly associated with small-cell lung carcinoma or breast carcinoma.¹² The best-supported pathophysiological mechanism by which a pancreatic metastasis triggers AP is mechanical obstruction of the pancreatic duct caused by tumor infiltration or extrinsic compression, leading to intraglandular enzymatic activation.¹² The clinical case accompanying this review vividly illustrates this uncommon presentation: A 51-year-old man with severe epigastric pain and a marked elevation of pancreatic enzyme levels (a serum lipase level of 759 U/L). His clinical presentation represented the acute manifestation of PM from an intimal sarcoma. In this setting, AP should not be automatically attributed to common causes such as biliary disease or alcohol consumption in patients with a history of malignancy.¹²

5.2. Differential diagnosis

The main diagnostic challenge is to distinguish PM from primary PDAC. The main distinguishing clinical, radiological, and pathological features are summarized in [Table 1](#). PDAC accounts for approximately 90% of all solid pancreatic masses.^{1,8,9} Other critical differential diagnoses include pancreatic neuroendocrine tumors (PanNETs) and solid pseudopapillary neoplasms.^{1,7,19}

Table 1. Differential diagnosis of PM, PDAC, and PanNET

Variable	PM	PDAC	PanNET	Evidence base
Clinical history	Remote or concurrent history of extrapancreatic malignancy (e.g., nephrectomy for renal cell carcinoma) ^{2,12} ; often associated with a long disease-free interval (median 7–10 years for renal cell carcinoma). ^{1,2,5,7,12}	No previous malignancy; risk factors include smoking, obesity, diabetes, and heavy alcohol consumption. ⁸	Usually sporadic but can be associated with genetic syndromes such as MEN1 or von Hippel–Lindau. ²⁰	Comprehensive review, systematic reviews, multicenter clinicopathological studies, and pathology-based studies.

(Cont'd...)

Table 1. (Continued)

Variable	PM	PDAC	PanNET	Evidence base
Clinical presentation	Frequently asymptomatic (40%–70%) and detected incidentally during surveillance imaging. ^{2,5,12,14} Rarely presents as acute pancreatitis.	Commonly presents with progressive systemic symptoms: weight loss, anorexia, pain, and jaundice (if occurs in the head). ⁸	May be asymptomatic or present with specific hormonal syndromes if functional (e.g., insulinoma, gastrinoma). ²⁰	Comprehensive, systematic, and narrative reviews; acute pancreatitis supported mainly by case reports and small case series.
CT findings	Solitary mass (74%) with well-defined margins. ^{2,7,12,14} Multifocality is common (30%–40%) and strongly suggests a renal origin. ^{7,14}	Typically a solitary mass with indistinct, infiltrative margins. ⁸	Well-circumscribed, typically solitary masses with a homogeneous enhancement pattern. ²⁰	Comprehensive, systematic, and narrative reviews, supported by multicenter observational studies.
MRI findings	Well-defined lesions, typically demonstrating hyperintensity on T2-weighted sequences. ^{2,7}	Hypovascular infiltrative pancreatic mass on MRI. ⁸	Well-circumscribed hypervascular lesions on MRI. ²⁰	Comprehensive review and a multicenter observational study; MRI-specific findings are based on limited retrospective imaging data.
PET/CT findings	¹⁸ F-FDG avidity is variable (high in sarcomas, inconsistent in renal cell carcinoma). ^{2,7}	Typically positive for ¹⁸ F-FDG uptake. ⁸	⁶⁸ Ga-DOTATATE typically shows high avidity in well-differentiated tumors. ²⁰ ¹⁸ F-FDG uptake is variable. ²⁰	Comprehensive review and a multicenter observational study; PET/CT findings vary according to the primary tumor.
Vascular pattern	Characteristic hypervascularity in renal cell carcinoma and melanoma. ^{7,12,14,21} Lung and colon metastases are typically hypovascular. ^{16,21}	Characteristically hypovascular and hypo-attenuating relative to the surrounding pancreatic parenchyma. ⁸	Characteristically hypervascular with arterial enhancement. ²⁰	Systematic and narrative reviews, supported by retrospective observational imaging studies.
Pancreatic duct involvement	Main pancreatic duct dilation is uncommon unless the tumor is bulky or causes direct mechanical compression. ^{7,13,14}	Very common; the “double duct sign” (simultaneous biliary and pancreatic duct obstruction) is highly suggestive of pancreatic ductal adenocarcinoma. ⁸	Obstruction of the pancreatic duct is uncommon. ²⁰	Systematic and narrative reviews, supported by multicenter observational studies.
Typical EUS appearance	Hypoechoic, oval-shaped lesions with well-defined borders. ^{14,16} Predominantly hypervascular on Doppler evaluation. ^{14,16,21}	Solid hypoechoic mass with irregular borders and early tendency to invade nearby structures. ²² Typically hypovascular on Doppler evaluation. ²²	Solid hypoechoic oval lesions with well-defined borders and a hypervascular pattern. ^{20,22}	Mainly based on retrospective EUS studies and systematic review evidence.
Main immunohistochemical markers	Site-specific markers: Renal (PAX8 ⁺ , CD10 ⁺ , CAIX ⁺); Lung (TTF-1 ⁺ , Napsin A ⁺); Colorectal (CDX2 ⁺ , SATB2 ⁺); Breast (GATA3 ⁺ , ER/PR ⁺). ^{13,14,16}	Typically expresses epithelial immunohistochemical markers, with loss of SMAD4 observed in a subset of cases. ^{8,22}	Typically expresses neuroendocrine immunohistochemical markers, including chromogranin A and synaptophysin. ^{20,22}	Systematic and narrative reviews, supported by clinicopathological studies.
Diagnostic clues	Documented history of extrapancreatic malignancy. ^{10,11,23} Well-defined imaging margins and multifocality, particularly in renal cell carcinoma. ^{2,7,14,23}	Hypovascular mass on CT with irregular borders and early ductal obstruction or distal pancreatic atrophy. ⁸	Functional hormonal symptoms. ²⁰ Homogeneous hypervascularity and somatostatin receptor imaging (DOTATATE) positivity. ^{20,22}	Comprehensive review, systematic reviews, pooled analysis, and multicenter clinicopathological studies.

Note: Evidence for PDAC and PanNET is primarily derived from current ESMO Clinical Practice Guidelines^{8,20} and the referenced pathology review²², unless otherwise indicated.

Abbreviations: ¹⁸F-FDG: Fluorine-18 fluorodeoxyglucose; ⁶⁸Ga-DOTATATE: Gallium-68 DOTATATE; CAIX: Carbonic anhydrase IX; CD: Cluster of differentiation; CDX2: Caudal-type homeobox 2; CT: Computed tomography; ER: Estrogen receptor; EUS: Endoscopic ultrasound; GATA3: GATA-binding protein 3; MEN1: Multiple endocrine neoplasia type 1; MRI: Magnetic resonance imaging; PAX8: Paired box gene 8; PDAC: Pancreatic ductal adenocarcinoma; PET: Positron emission tomography; PM: Pancreatic metastasis; PanNET: Pancreatic neuroendocrine tumor; PR: Progesterone receptor; SATB2: Special AT-rich sequence-binding protein 2; SMAD4: SMAD family member 4; TTF-1: Thyroid transcription factor-1.

- Margins and morphology: Unlike PDAC, which typically presents with irregular infiltrative margins, PM are usually characterized by well-defined and sharply demarcated borders, a feature that may represent an important diagnostic clue in imaging studies.^{1,7}
- Differentiation from PanNETs: Metastases from RCC and melanoma are characteristically hypervascular, necessitating careful differentiation from PanNETs.^{1,2,7}

5.3. Radiological findings and positron emission tomography/computed tomography

Multiphasic CT is the standard imaging modality for the characterization of PM.^{2,7,24} PM most commonly present as solitary masses in 70%–74% of cases; however, multifocal pancreatic lesions strongly suggest a renal primary tumor as their origin.^{4,7,10}

- Vascular patterns: During the arterial phase of CT, RCC and melanoma typically demonstrate avid contrast enhancement (hypervascular lesions), whereas metastases from lung, colorectal, or breast cancer are usually hypovascular, closely mimicking the imaging pattern of primary PDAC.^{1,2,7}
- Role of PET/CT: ¹⁸F-FDG avidity is variable. ¹⁸F-FDG PET/CT is particularly useful for detecting aggressive tumors such as sarcomas or lung cancer, whereas ¹⁸F-FDG uptake is inconsistent and may be absent in RCC.^{1,2,24} In the patient with PAIS presented in this review, PET/CT was crucial for demonstrating the hypermetabolic activity of both the pancreatic lesions and the pulmonary artery mass, thereby supporting the suspicion of metastatic disease and prompting reconsideration of the initial diagnosis of PTE. However, the definitive diagnosis was established histologically by core needle biopsy of the pulmonary lesion.

5.4. Endoscopic ultrasound and tissue acquisition

Endoscopic ultrasound (EUS)-guided tissue acquisition has become the gold standard for definitive diagnosis of PM, with a reported diagnostic accuracy of up to 97.9%.^{1,4,7} On endoscopic ultrasonography, PM typically appear as hypoechoic, round, or oval lesions with well-defined margins.⁷

- Fine-needle biopsy versus fine-needle aspiration: EUS-FNB is preferred over fine-needle aspiration, as it provides core tissue specimens with preserved architectural structure rather than isolated cells alone. This is critical for facilitating detailed histopathological evaluation and the performance of multiple immunohistochemical stains without exhausting the tissue sample.^{7,22}

5.5. Histopathology and immunohistochemistry

Histopathological examination is imperative because of the marked morphological overlap between PM and primary pancreatic neoplasms.^{1,2,23} The use of a targeted immunohistochemical panel represents the cornerstone for determining the primary site of origin:

- Renal origin: Positivity for paired box gene 8 (PAX8), cluster of differentiation 10 (CD10), carbonic anhydrase IX (CAIX), and vimentin, coupled with consistently negative staining for neuroendocrine markers (chromogranin and synaptophysin).¹
- Pulmonary origin: Expression of thyroid transcription factor 1 (TTF-1) and napsin A (in adenocarcinoma), or specific markers of small-cell carcinoma.¹
- Colorectal origin: Expression of caudal-type homeobox 2 (CDX2) and special AT-rich sequence-binding protein 2 (SATB2).¹
- Sarcomas: Identified by spindle-cell morphology coupled with subtype-specific mesenchymal markers.¹ The presented case of PAIS in this review highlights the importance of tissue diagnosis. Although the pancreatic lesions were suggestive of metastatic disease in view of the patient's pulmonary history, histological confirmation prevented the patient from being misclassified as having primary pancreatic cancer and allowed tumor-specific systemic chemotherapy to be initiated. Following initiation of systemic chemotherapy for metastatic pulmonary artery intimal sarcoma, the patient's AP resolved. Although the temporal sequence is compatible with treatment-related clinical improvement, causality cannot be established from a single case, and alternative explanations cannot be excluded.

6. Therapeutic management strategies

The therapeutic approach to PM has evolved from a purely palliative perspective toward a multidisciplinary and personalized strategy, in which treatment intensity is determined by the biology of the primary tumor, the metastatic burden, and the patient's functional status.^{2,13}

6.1. Surgical management: Pancreatic metastasectomy

Surgery offers the greatest potential for long-term disease-free survival in patients with isolated pancreatic metastatic disease.^{2,10,12}

In high-volume medical centers, pancreatectomy for metastatic disease has been shown to be a safe procedure, with very low operative mortality rates ranging from 1% to 3.4%.^{10–12} Nevertheless, postoperative morbidity remains substantial, occurring in approximately 38%–40% of

patients, a rate comparable to that reported after pancreatic resection for primary tumors.^{10–12,21}

- Types of resection: Distal pancreatectomy is the most frequently performed procedure (63.7%), owing to its greater technical feasibility and lower morbidity compared with pancreaticoduodenectomy (30%).^{10–12} Total pancreatectomy is generally reserved for patients with diffuse multifocal disease (11.4%).^{10,12}
- Extent of resection: An ongoing debate exists between standard pancreatic resections and parenchyma-sparing procedures, such as enucleation or central pancreatectomy.^{10,12,16} Although the latter reduces the risk of exocrine and endocrine insufficiency, including postoperative diabetes mellitus, some authors have reported higher rates of local recurrence and postoperative pancreatic fistula (23% versus 14% following conventional surgery).^{10,12,16}
- Repeat metastasectomy: One of the most important findings from contemporary series is that repeat surgery for isolated recurrence within the remnant pancreas is a valid therapeutic strategy that independently improves overall survival rate ($p = 0.003$), particularly in patients with RCC.^{10,13,14}

6.2. The oligometastatic disease paradigm

Current therapeutic strategies are based on the concept of oligometastatic disease, generally defined as the presence of ≤ 3 –5 resectable metastatic lesions.^{13,14} In this setting, systemic therapy may be used as a biological “test of time” to identify patients with less aggressive disease before undertaking major surgical resection. In patients with RCC, treatment using tyrosine kinase inhibitors and immune checkpoint inhibitors plays a central role.^{2,14} However, emerging biological evidence suggests that PM from RCC exhibit an angiogenic but “immune-quiescent” microenvironment characterized by low inflammatory activity, which might explain their relatively lower sensitivity to immunotherapy compared with other metastatic sites, thereby reinforcing the role of local surgical treatment.^{2,14}

6.3. Systemic treatment and palliation

In non-renal malignancies, such as lung cancer, colorectal cancer, or sarcomas, survival following surgical resection is considerably low. Consequently, therapeutic management generally prioritizes tumor-specific systemic chemotherapy according to the primary malignancy diagnosed.^{2,10,13,21}

Stereotactic body radiotherapy has emerged as a potential option for local disease control in patients who are not suitable candidates for surgery because of comorbidities or advanced disease burden, although the evidence

supporting its use in PM remains limited compared with other metastatic sites.^{13,14,24} For palliation of obstructive symptoms, techniques such as endoscopic biliary or duodenal stenting and transhepatic porto-mesenteric venous stenting can provide significant symptomatic relief with low procedure-related morbidity.^{22,25}

6.4. Comparison with the clinical case

The management of the patient with PAIS illustrates both the application of and deviation from the therapeutic principles described above.

- Biological priority: In contrast to the indolent biological behavior of RCC, PAIS is a rapidly disseminating malignancy. The presence of multiple hypermetabolic lesions coupled with extensive vascular involvement in the patient discouraged upfront metastasectomy, leading to prioritization of systemic disease control.
- Management of complications: Following systemic chemotherapy, the patient’s abdominal pain resolved, and serum lipase levels returned to normal. Although this temporal association is consistent with clinical improvement following treatment of the underlying malignancy, it does not establish that reduction in tumor burden or relief of pancreatic duct obstruction was solely responsible for the resolution of pancreatitis. Alternative explanations, including spontaneous resolution of AP and partial improvement of paraneoplastic inflammatory processes independent of local tumor mechanics, cannot be excluded.¹² Nevertheless, the present case suggests that effective systemic therapy may contribute to clinical improvement in selected patients with PM presenting with AP, potentially reducing the need for invasive local interventions in advanced systemic disease.^{12,13}
- Future therapeutic perspectives: Although anthracycline-based chemotherapy currently represents the standard systemic treatment for disseminated PAIS, recent molecular characterization has identified recurrent *MDM2* amplification, frequently associated with *CDK4* and *PDGFRA* alterations, as the molecular hallmark of this disease. These findings have prompted the investigation of the efficacy of targeted therapies and immune checkpoint inhibitors in selected molecular subgroups, particularly tumors with microsatellite instability-high (MSI-H) phenotype or programmed death-ligand 1 (PD-L1) expression. Although these approaches remain investigational and were not applicable to the present patient, they illustrate the ongoing transition toward more personalized treatment strategies that might further refine the management of PM developing from rare sarcomas in the future.¹⁵

7. Prognosis and predictive factors

The prognosis of PM has undergone substantial reassessment in the contemporary literature, moving away from the historical perception of representing a terminal event toward a disease with the potential for prolonged survival in selected patients.^{2,13}

7.1. Main prognostic factors identified

Several key determinants that significantly impact overall survival have been identified through available evidence:

- **Primary tumor origin:** This is the most prominent and consistent prognostic factor across all published studies.^{2,10–12} RCC is associated with the most favorable prognosis, with median postoperative survival of 116 months and 5-year survival rates up to 76.6%.^{11,13,14,21} In contrast, primary tumors such as lung cancer, colorectal cancer, and sarcomas are associated with significantly poorer prognosis, with reported 5-year survival rates generally ranging from 15% to 22%.^{10,12,13,21}
- **Molecular profile:** Beyond the anatomical origin of the primary malignancy, the molecular landscape is increasingly recognized as an important determinant of prognosis and treatment selection. Recurrent amplification of *MDM2*, frequently associated with *CDK4* and *PDGFRA* amplification, represents the characteristic molecular hallmark of the disease and might contribute to the aggressive biological behavior of intimal sarcoma. Although these molecular alterations have not yet been specifically validated as independent prognostic factors in PM, they are becoming increasingly relevant for guiding systemic treatment through molecularly informed therapeutic strategies, including targeted therapies and immunotherapy in selected patients.¹⁵
- **Extrapaneatic disease:** The presence of metastatic disease outside the pancreas at the time of diagnosis is an independent predictor of poor prognosis.^{10–12} Median survival of 45 months has been reported in patients with isolated pancreatic disease, compared with 26 months in those with additional metastatic sites.^{10–12} Nevertheless, some authors suggest that surgical resection remains an appropriate option when all extrapaneatic lesions are amenable to complete resection with curative intent (R0 resection).^{10–12}
- **Presence of symptoms:** Asymptomatic patients diagnosed through radiological surveillance protocols have reported to have significantly better survival outcomes.^{10–12} Conversely, the presence of symptoms, such as abdominal pain or obstructive jaundice, usually reflects a greater tumor burden and more aggressive tumor biology.^{10–12}

- **DFI:** A prolonged interval between treatment of the primary tumor and the development of PM, particularly when exceeding three years, is considered a marker of indolent tumor biology and is associated with more favorable oncological outcomes.^{10–12}

7.2. Relationship to the clinical case

The case of the patient with PAIS illustrates the coexistence of several adverse prognostic factors identified in the literature.

- **Unfavorable histology:** PAIS is a highly malignant neoplasm, contributing to lower survival compared with RCC.
- **Acute symptomatic presentation:** Presentation as AP represents an exceptionally symptomatic mode of onset which, according to the literature, is associated with a more aggressive clinical course.^{10,12}
- **Systemic disease:** The presence of multiple synchronous lesions in both the lungs and the pancreas places this case beyond the conventional definition of isolated oligometastatic disease, thereby justifying a therapeutic strategy focused primarily on systemic disease control.

7.3. Strengths and limitations of the available evidence

The available evidence has several important strengths but is also subject to substantial methodological limitations that should be considered when interpreting the reported outcomes.

- **Strengths:** The availability of pooled individual-patient data analyses, such as that by Zhou *et al.*¹¹, which included 436 patients, has provided a substantially larger evidence base for identifying prognostic factors in RCC. In addition, there is a strong consensus regarding the safety of pancreatic surgery when performed in specialized referral centers.^{10,12}
- **Limitations:** Most of the available evidence is derived from retrospective studies, which introduces substantial selection bias toward patients with better performance status and less advanced disease, potentially leading to an overestimation of the true benefit of surgery.^{10,12,16} There is also a critical lack of prospective randomized studies comparing pancreatic metastasectomy with contemporary systemic therapies, including tyrosine kinase inhibitors and immunotherapy. Furthermore, evidence relating to rare tumors such as intimal sarcoma is limited to case reports or very few case series, making it difficult to generalize current therapeutic recommendations.^{2,10,11,15}

8. Critical discussion and clinical implications

This discussion integrates the available literature with the insights from the clinical case of a patient with PAIS and AP, examining how this exceptional presentation challenges and expands current paradigms of PM.

8.1. Opposite ends of the biological spectrum: From renal cell carcinoma to intimal sarcoma

Oncological literature identifies RCC as the predominant model of PM, accounting for 30%–70% of reported PM, characterized by an indolent clinical course and a latency period that may exceed two decades.^{2,5,10,12} RCC exemplifies the “seed and soil” hypothesis, demonstrating selective organotropism that may facilitate the development of isolated oligometastatic disease.^{2,14} In striking contrast, intimal sarcoma lies at the opposite end of the biological spectrum: An exceedingly rare and highly aggressive vascular malignancy characterized by rapid and synchronous hematogenous dissemination.^{10,12}

The clinical case provides unique evidence by documenting how this type of sarcoma may initially mimic benign vascular disorders, such as PTE, and delays the correct diagnosis until the onset of an acute complication reveals the true systemic nature of the disease. This observation highlights the need to reconsider the threshold for clinical suspicion in patients presenting with pulmonary vascular masses displaying atypical behavior.¹⁰

8.2. Acute pancreatitis: More than a complication, a warning sign

Although 40%–70% of PM are asymptomatic, presentation as AP is an exceptionally rare event, as it is conventionally associated with lung or breast carcinoma.^{10,12,26}

- Pathophysiological analysis: The mechanical basis of AP secondary to PM is generally attributed to pancreatic duct obstruction caused by direct tumor infiltration or extrinsic compression.^{10,12} Although pancreatic duct obstruction remains the best-supported mechanism described in the literature, other explanations, including spontaneous resolution of pancreatitis, paraneoplastic inflammatory mechanisms, or vascular injury unrelated to ductal obstruction, cannot be excluded. In the present case, the vascular biology of intimal sarcoma raises the hypothesis that vascular mechanisms beyond pancreatic duct obstruction might have contributed to pancreatic injury. However, due to the absence of direct radiological, laboratory, or histopathological evidence of pancreatic microvascular involvement, this proposed mechanism remains speculative and should be regarded solely as a hypothesis to be

investigated in the future. Similarly, although AP resolved after initiation of systemic chemotherapy in the present patient, this temporal relationship should not be interpreted as confirmation of the proposed pathogenic mechanism. The observed clinical improvement might be due to multiple concurrent factors, including spontaneous resolution of pancreatitis, treatment of paraneoplastic inflammatory processes, or reduction of tumor burden with partial relief of local pancreatic injury. Because there is no direct evidence establishing the relative contribution of these mechanisms, the observed clinical course should be regarded as hypothesis-generating rather than definitive evidence of causality.¹²

- Diagnostic implications: This case demonstrates that AP of uncertain etiology in a patient with a history of malignancy or suspicious pulmonary masses should not automatically be attributed to biliary lithiasis. Instead, the possibility of metastatic disease occurrence should be considered promptly, by incorporating both EUS-FNB and ¹⁸F-FDG PET/CT into the diagnostic work-up.^{1,2,11}

8.3. Therapeutic controversies and biological timing

There is a strong consensus regarding the benefit of pancreatic metastasectomy in RCC, which is the ability to achieve prolonged survival even in the presence of recurrent disease.^{10,11,13} However, the role of surgery in sarcomas remains considerably more controversial because of their high rate of early systemic recurrence.^{2,10}

The response of the patient in our review to systemic chemotherapy, characterized by normalization of serum lipase levels and complete resolution of abdominal pain, supports a treatment strategy that prioritizes systemic disease control in highly malignant tumors, rather than the current tendency toward universally aggressive surgical management. These findings suggest that the management of PM should be guided primarily by tumor biology—including the DFI, histology, and response to previous treatment—rather than by anatomical resectability alone.²

8.4. Methodological limitations and future directions

This review highlights several important knowledge gaps in the current literature. First, there is no universally accepted definition of pancreatic oligometastatic disease. Although surgery is generally accepted for multiple pancreatic lesions in RCC, its role in other malignancies remains uncertain.^{13,14} Second, the role of immunotherapy has yet to be clearly defined, as pancreatic metastases from RCC appear to exhibit an “immune-quiescent” stromal microenvironment.^{2,14}

Another important limitation of the current evidence is the reliance on conventional analytical approaches to investigate a biologically heterogeneous and clinically complex disease. Recent advances in machine learning have shown considerable potential to identify complex biological relationships and predictive patterns that may remain undetected using conventional statistical methods.^{17,27,28} Although these computational methodologies have not yet been systematically applied to PM because of the rarity of the disease and the limited availability of sufficiently large datasets, future integration of clinicopathological, molecular, and imaging data could facilitate biomarker discovery, patient stratification, and prediction of metastatic behavior. Furthermore, complementary computational modeling and simulation approaches may support the biological interpretation of experimental and clinical observations, provide additional mechanistic insights into metastatic dissemination, and facilitate the development of more individualized therapeutic strategies.^{27,28}

Finally, the available evidence suggests that the conventional 5-year follow-up period is insufficient. Given the well-described phenomenon of tumor dormancy, lifelong surveillance extending beyond 10–15 years has been proposed to ensure that therapeutic opportunities are not missed when these lesions are detected at an early stage.^{2,10}

9. Conclusion

Pancreatic metastases remain an uncommon but clinically important entity that should be considered in patients with current or previous history of malignancy presenting with pancreatic lesions or unexplained AP. Accurate diagnosis requires integration of clinical history, multimodal imaging, EUS-guided tissue acquisition, and immunohistochemical characterization to distinguish secondary tumors from primary pancreatic neoplasms and to inform appropriate management.

Treatment should be individualized according to the biology of the primary tumor, disease burden, and patient fitness. While pancreatic metastasectomy offers favorable long-term outcomes in carefully selected patients, particularly those with RCC, systemic therapy remains the cornerstone of treatment for aggressive malignancies with disseminated disease. The present case of PAIS presenting as AP highlights an exceptionally rare clinical scenario and underscores the importance of maintaining a high index of suspicion, adopting a multidisciplinary approach, and ensuring long-term radiological surveillance in selected patients.

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Author contributions

Conceptualization: Luis Cabezón-Gutiérrez, Fátima Carrasco-Valero

Investigation: José Ramón Sevilla-Resúa, Maria Carmen Montero-Hernández

Project administration: Luis Cabezón-Gutiérrez

Resources: Sheherezade Gallego-Nieto, José Ramón Sevilla-Resúa

Validation: Maria Carmen Montero-Hernández

Writing—original draft: Fátima Carrasco-Valero

Writing—review & editing: Luis Cabezón-Gutiérrez, Indra D. Sanoja-Fernández, Sara Custodio-Cabello, Beatriz Chacón-Ovejero, Sheherezade Gallego-Nieto, José Ramón Sevilla-Resúa, Maria Carmen Montero-Hernández

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