UNIVERSITY OF PADUA

SCHOOL OF MEDICINE

Single-Cycle Master's Degree Course in Medicine and Surgery

Department of General Surgery

THESIS

PATTERN OF RECURRENCE AFTER PANCREATECTOMY AND ONCOLOGICAL TREATMENT (POCEMON) FOR PANCREATIC DUCTAL ADENOCARCINOMA

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Co-supervisor Dr. Aya Maekawa

Graduand: Giulia Cemin

Academic Year 2025-2026

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1. Abstract

1.1. Background

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most aggressive and lethal malignancies worldwide, with extremely poor long-term survival despite continuous advances in surgical and oncological treatment. Even after curative-intent resection, recurrence develops in up to 80% of patients within the first two years following surgery, representing the main determinant of prognosis.

Patterns of recurrence after PDAC resection are highly heterogeneous and appear to reflect different biological behaviors of the disease.
Liver metastases, which occur in approximately 30–50% of patients, are the most common form of relapse and are generally associated with aggressive disease progression and poor survival outcomes. Lung metastases, observed in around 10–20% of cases, are increasingly recognized as a distinct subgroup characterized by a slower disease course and improved post-recurrence survival, especially in selected patients eligible for surgery or stereotactic body radiotherapy (SBRT). Locoregional recurrence, involving the retroperitoneum or pancreatic bed, occurs in approximately 20–30% of patients and is associated with technically challenging management and limited survival. Peritoneal and multi-site recurrence typically indicate diffuse systemic disease and carry the poorest prognosis.

An additional clinical challenge is represented by biochemical recurrence, defined as a progressive increase in tumor markers in the absence of radiological evidence of disease. Although this pattern is increasingly recognized in clinical practice, its optimal management remains poorly standardized.

The growing adoption of neoadjuvant therapy has also modified recurrence dynamics and may influence both recurrence timing and metastatic distribution, although its overall impact on recurrence biology remains incompletely understood. In this context, a better understanding of recurrence patterns and

post-recurrence management strategies is essential to improve patient selection and optimize therapeutic decision-making.

1.2. Aim of the study

This retrospective multicenter study investigates recurrence patterns and management strategies following curative-intent resection for pancreatic ductal adenocarcinoma (PDAC), with particular focus on recurrence site, timing, biological behavior, and therapeutic approaches adopted in clinical practice.

A comparative analysis between patients treated with neoadjuvant therapy and those undergoing upfront surgery was performed in order to evaluate potential differences in recurrence dynamics and survival outcomes. Particular attention was dedicated to post-recurrence management, including systemic therapy, surgery, stereotactic radiotherapy, and other local treatment strategies, as well as to challenging scenarios such as biochemical recurrence without radiological evidence of disease.

The primary objectives of the study were to characterize recurrence patterns and evaluate treatment strategies and outcomes after recurrence. Secondary objectives included the comparison of recurrence patterns between treatment groups, the analysis of survival according to recurrence type, the evaluation of biochemical recurrence management, and the identification of factors associated with aggressive post-recurrence treatment.

1.3. Materials and methods

This retrospective multicenter observational cohort study was conducted according to the STROBE guidelines and included patients treated at high-volume pancreatic cancer centers.

Patients who underwent curative-intent resection for histologically confirmed pancreatic ductal adenocarcinoma (PDAC) between January 2015 and December 2023 were considered eligible, proved they had no metastatic disease at the time of surgery, available baseline imaging and CA19-9 measurements, and at least 18 months follow-up.

Patients were stratified according to treatment strategy into neoadjuvant therapy and upfront surgery groups. Tumor resectability was assessed by institutional multidisciplinary teams (MDTs) according to National Comprehensive Cancer Network (NCCN) guidelines, with the surgical goal of achieving complete macroscopic tumor removal through R0 or R1 resection.

Neoadjuvant treatment consisted of modern chemotherapy regimens with or without radiotherapy. Postoperative surveillance included clinical assessment, cross-sectional imaging, and serial CA19-9 monitoring. Recurrence was classified according to anatomical site, timing, and modality of detection, including both radiological recurrence and biochemical recurrence defined by isolated CA19-9 elevation.

The primary endpoint of the study was the characterization of recurrence patterns. Secondary endpoints included overall survival (OS), recurrence-free survival (RFS), post-recurrence survival (PRS), time to recurrence, and survival outcomes according to recurrence type and treatment strategy.

Statistical analyses were performed using Kaplan-Meier methods and Cox proportional hazards regression models. The overall study cohort comprised approximately 2500 patients from international centers.

1.4. Results

A total of 1176 patients who underwent curative-intent resection for pancreatic ductal adenocarcinoma (PDAC) between 2015 and 2023 were included in the preliminary POCEMON cohort analysis. During follow-up, recurrence developed in more than half of the patients, with liver recurrence representing the most frequent pattern, followed by locoregional and pulmonary recurrence. Significant differences emerged among recurrence types in terms of timing, CA19-9 levels, treatment allocation, and survival outcomes.

Pulmonary recurrence was associated with the longest recurrence-free interval, lower tumor marker levels at relapse, and the most favorable prognosis, particularly in patients eligible for local treatment strategies. In contrast, liver recurrence was characterized by earlier relapse, higher CA19-9 levels, and significantly poorer survival outcomes, reflecting a more aggressive biological behavior. Peritoneal and multi-site recurrences were similarly associated with diffuse disease and limited survival.

Local treatment strategies, including surgery and stereotactic body radiotherapy, were more commonly adopted in selected patients with lung and locoregional recurrence and were associated with prolonged post-recurrence survival compared with systemic therapy alone. However, multivariable analysis suggested that treatment selection and underlying tumor biology played a major role in determining prognosis.

1.5. Conclusions

Recurrence after curative-intent resection for PDAC is characterized by marked biological and prognostic heterogeneity according to recurrence pattern. Pulmonary recurrence appears to represent a distinct and more indolent disease phenotype associated with improved survival outcomes and greater applicability of aggressive local treatment strategies, whereas liver and disseminated recurrences remain associated with poor prognosis and predominantly systemic disease behavior.

These findings support the concept that recurrent PDAC should not be managed as a single clinical entity and highlight the importance of integrating recurrence pattern, disease-free interval, CA19-9 levels, disease burden, and patient performance status (ECOG) into post-recurrence therapeutic decision-making.

Although systemic chemotherapy remains the standard treatment for most patients, selected local therapies may provide meaningful survival benefit in highly selected cases within a multidisciplinary and biologically informed treatment strategy. Further prospective studies are needed to refine recurrence-pattern-specific management algorithms and improve patient selection for aggressive post-recurrence interventions.

2. Introduction

2.1. PDAC: definition and histology

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy arising from the epithelial cells of the pancreatic ductal system, representing the most common type of pancreatic cancer. Despite significant progress in oncology and surgery, PDAC continues to be associated with one of the worst prognoses among solid tumors.
Histologically, PDAC is characterized by irregular, infiltrative glandular structures with variable degrees of differentiation, ranging from well-differentiated to poorly differentiated or anaplastic forms.

A hallmark feature of PDAC is its marked desmoplastic stroma, generated by the interaction between tumor cells and the surrounding microenvironment. This dense fibrotic matrix contributes not only to tumor progression but also to treatment resistance by limiting drug penetration and promoting immune evasion (Figure 1). In addition, the tumor microenvironment is characterized by complex immunological interactions in which cytotoxic T-cell activity is often impaired and suppressed, while other lymphocyte subtypes may promote immune tolerance.

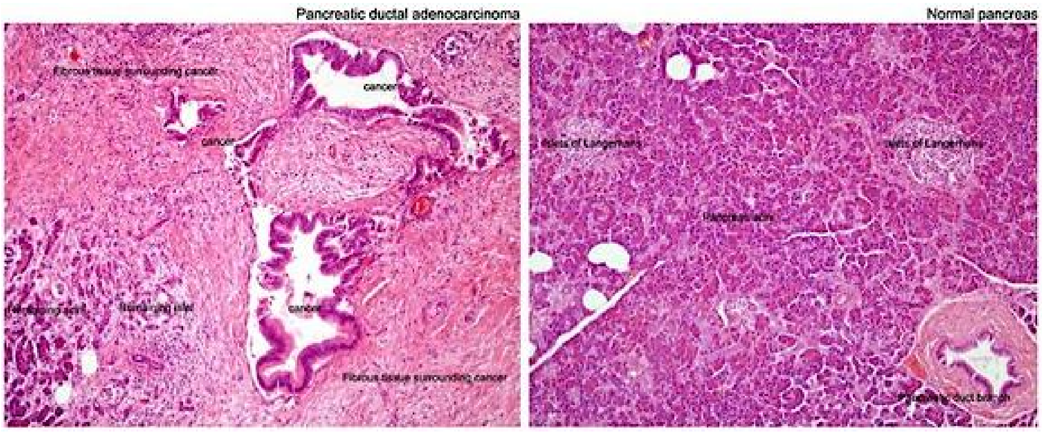


Figure 1 - Anatomy of the pancreas and main locations of pancreatic cancer

Another distinctive characteristic of PDAC is its tendency toward venotropism (vascular and perineural invasion), where tumor cells infiltrate and grow along vessel walls, facilitating early hematogenous dissemination, especially to the liver which represents the most frequent site of distant metastasis. Figure 2 illustrates a CT scan showing infiltration of the portal vein confluence by PDAC.

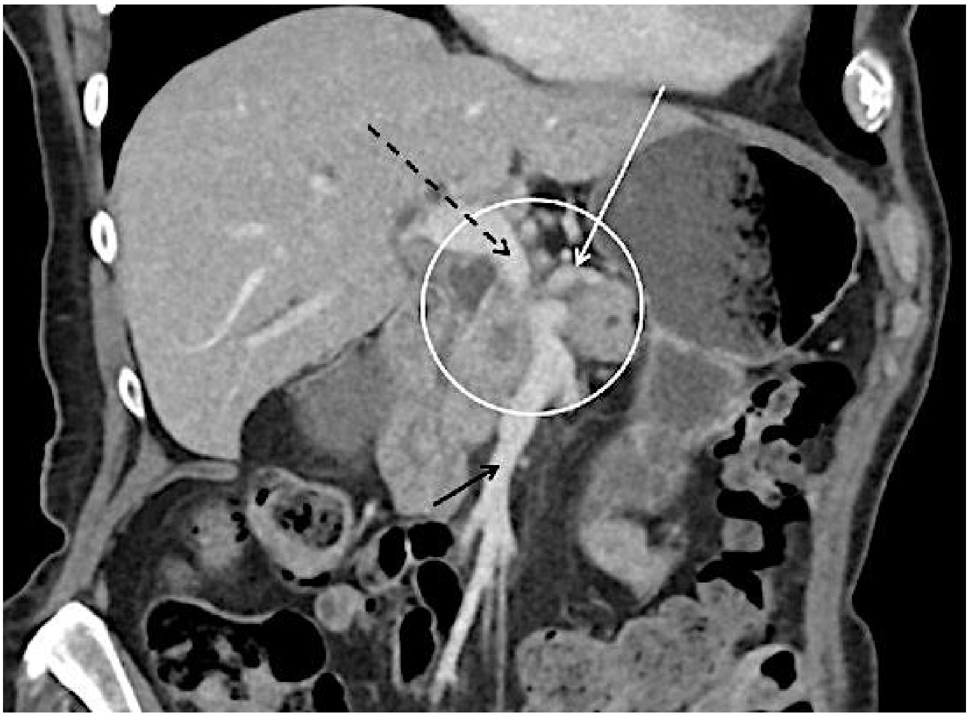


Figure 2 – Abdominal CT scan showing PDAC infiltration of the portal vein confluence (white circle). Superior mesenteric vein (black arrow), portal vein (broken black arrow), splenic vein (white arrow).

The extremely unfavorable prognosis associated with PDAC is largely related to its aggressive biological behavior, early metastatic potential, and the absence of effective screening strategies for the population. Furthermore, the disease often remains clinically silent during the early stages, leading to late diagnosis only after local advancement or metastatic spread has already occurred.

2.2. Epidemiology, risk factors and prognosis

Pancreatic cancer is currently one of the leading causes of cancer-related mortality worldwide, particularly in industrialized countries, where both incidence and mortality continue to rise steadily. Globally, it accounts for approximately 5% of all cancer-related deaths and in Europe and the United States is expected to rank among the top three causes of cancer-related death in the coming decades.

Despite advances in treatment, its incidence is rising by about 1.1% annually and the overall 5-year survival remains below 10% even after curative-intent resection, since approximately 70-80% of patients experience recurrence within 2 years. In Italy, approximately 14,000 new cases were estimated in 2020, with a slightly higher prevalence among males and greater incidence rates in northern regions.

Age represents the main non-modifiable risk factor for PDAC, whose incidence increases significantly with advancing age. Ethnicity also appears to influence disease prevalence, with African American populations showing higher incidence rates.

Other recognized and modifiable risk factors include smoking, which remains one of the strongest and most consistently recognized contributors, accounting for a substantial proportion of cases. Environmental exposures (e.g., asbestos, benzene), high BMI and obesity, low physical activity, diabetes mellitus and chronic pancreatitis are also associated with PDAC, particularly when newly diagnosed.

The relationship between alcohol consumption and PDAC remains less clearly defined, although chronic heavy alcohol intake may contribute indirectly through the development of chronic pancreatitis. Dietary factors have also been investigated, particularly processed meats and dairy products, although available evidence remains partially conflicting. Findings regarding vitamin D are inconsistent, and its potential role in the development of this disease remains to be clarified.

Persistent inflammation of the pancreas, as seen in chronic pancreatitis, contributes to tumor development. Individuals with a prior history of this condition have an approximately 7.2-fold higher risk of developing pancreatic cancer, while those with a familial predisposition may face an increase in risk of up to 82-fold, as do certain genetic alterations (e.g., BRCA1/2, PALB2, TP53) and inherited syndromes such as Peutz–Jeghers, Lynch syndrome and familiar malignant melanoma syndrome.

2.3. Signs and symptoms

The clinical presentation of PDAC largely depends on tumor location within the pancreas.

Tumors arising from the pancreatic body and tail often remain asymptomatic for prolonged periods and are therefore frequently diagnosed at advanced stages. When symptoms occur, they usually include abdominal discomfort, back pain caused by involvement of surrounding structures, including the celiac plexus. Compression of adjacent organs may lead to dyspepsia, early satiety, nausea, or weight loss.

On the other hand, tumors located in the pancreatic head, present with symptoms that vary in relation to their distance from the Wirsung duct and pancreatic common duct. Frequently, they show up with painless jaundice due to bile duct obstruction. Other possible manifestations include acute pancreatitis secondary to pancreatic duct obstruction, bowel habit changes, progressive weight loss, anorexia, and new-onset diabetes – mainly due to the pancreatic exocrine disfunction.

Paraneoplastic syndromes may occasionally occur and can even precede diagnosis. These include thromboembolic phenomena such as Trousseau syndrome, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and neurological manifestations.

Unfortunately, early-stage PDAC is frequently asymptomatic or associated with nonspecific symptoms, contributing to delayed diagnosis and advanced disease presentation in the majority of patients.

2.4. Diagnostic workup

The diagnostic evaluation of patients with suspected PDAC requires a multidisciplinary approach involving surgeons, oncologists, radiologists, gastroenterologists, endoscopists, and pathologists.

Initial assessment relies on high-quality imaging, staging, and treatment planning. Contrast-enhanced computed tomography (CT) with pancreas-specific protocol remains the gold standard for initial evaluation and resectability assessment, particularly regarding vascular involvement of major arterial and venous structures.

Resectability status	Metastasis status	Arterial	Venous
Resectable	No distant metastases	No arterial involvement i.e. clear fat planes around the CA, SMA, and HA	Tumour not abutting SMV or PV or <180 contact without any distortion of venous shape/thrombosis
Borderline resectable	No distant metastases	Pancreatic head/uncinate tumour-SMA encasement <180° circumference of the vessel wall Pancreatic body/tail- CA encasement <180°circumference of the vessel wall	Venous involvement of the SMV or PV with >180 degrees of contact Or contact of <180 but with contour irregularity or thrombosis provided suitable vessel proximal and distal to the area of tumour involvement is available, allowing safe resection and reconstruction
Unresectable	Distant metastasis present including non regional lymph nodes involvement	Pancreatic head/uncinate tumour-SMA or CA encasement >180°, Pancreatic body/tail- SMA or CA encasement >180° Aortic invasion or encasement	Unreconstructible occlusion of the SMV or PV

Table I - Resectability status criteria from NCCN

Magnetic resonance imaging (MRI) may provide superior characterization of pancreatic parenchyma and ductal anatomy, although CT continues to represent the primary imaging modality for surgical planning.

Endoscopic ultrasound (EUS) is another key diagnostic tool and is particularly valuable for tissue acquisition through fine-needle aspiration or biopsy. In addition to histological confirmation, EUS allows accurate evaluation of periampullary lesions and pancreatic cystic neoplasms.

Positron emission tomography (PET) may be useful in selected cases, especially when metastatic disease is suspected but not clearly demonstrated on conventional imaging.

In patients at high risk of occult metastatic disease, staging laparoscopy may also be considered, particularly in the presence of markedly elevated CA19-9 levels, suspicious lymphadenopathy, or highly symptomatic disease.

Histological confirmation is generally required before neoadjuvant therapy but may not always be mandatory before upfront surgery in clearly resectable disease. EUS-guided biopsy is the preferred method, although false negatives may occur due to the desmoplastic nature of the tumor.

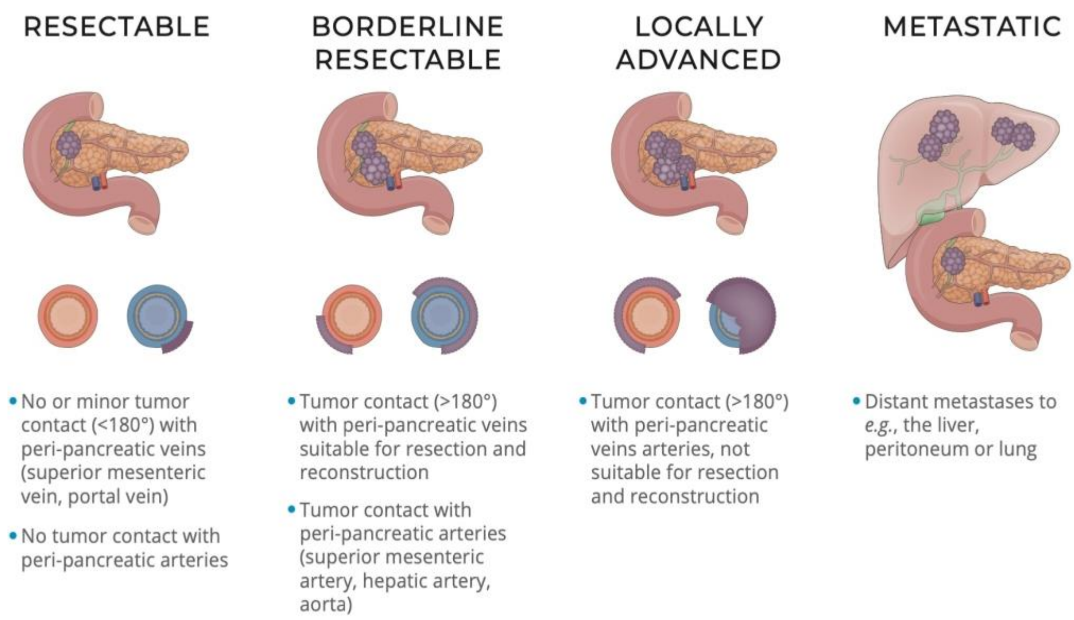


Figure 3 - Schematic representation of pancreatic cancer development.

Among serum biomarkers, Carbohydrate Antigen (CA 19-9) remains the most widely used marker in PDAC. Although it lacks specificity, CA19-9 plays an important role in diagnosis, prognostic stratification, treatment monitoring, and postoperative surveillance. It is measured in blood along with other markers, as CEA and CA-125 that may provide additional information.

Elevated CA19-9 levels may also be observed in benign conditions such as cholestasis or pancreatitis, as well as in other biliary or gastrointestinal malignancies. Furthermore, approximately 10% of Caucasian individuals do not express the sialyl-Lewis A antigen and are therefore unable to produce detectable CA19-9 levels. Thus, its median diagnostic performance includes a sensitivity of 79% and a specificity of 82%.

Despite these drawbacks, this marker retains value in the diagnostic work-up when used alongside other assessments and provides prognostic information. Higher baseline concentrations are associated with poorer outcomes and reduced overall survival. Beyond diagnosis and prognosis, it is widely employed to monitor treatment response and during post-therapy surveillance.

2.5. Treatment and current management of PDAC

Treatment strategies for PDAC are primarily determined by tumor resectability and metastatic condition.

As noted previously, surgical resection remains the only potentially curative option for patients without distant metastatic disease. The main surgical objective is complete tumor removal with negative margins (R0 resection), along with appropriate lymphadenectomy. However, the complicated anatomical relationships between the pancreas and surrounding vascular structures, makes particularly difficult to ensure complete tumor excision without leaving either visible or microscopic remnants; as a result R1 resections remain relatively common.

The increasing adoption of neoadjuvant therapy has significantly modified the management of PDAC, particularly in borderline resectable and locally advanced disease. Preoperative treatment aims to downstage tumors, reducing the likelihood of incomplete (R1) resections and facilitating a more radical surgical approach. It is therefore recommended for patients at higher risk of margin-positive resection, with the aim of improving resectability and increasing R0 rates.

Commonly adopted regimens include FOLFIRINOX or Gemcitabine combined with Nab-Paclitaxel, administered with or without radiotherapy.

The adoption of preoperative therapy has led to improved R0 resection rates, enabled surgical conversion in selected cases with vascular involvement, and contributed to moderate gains in overall survival. Nevertheless, its role in clearly resectable pancreatic ductal adenocarcinoma remains controversial and continues to be a matter of ongoing debate.

Restaging after neoadjuvant treatment remains challenging, due to the difficulty in distinguish between true tumor regression - characterized by fibrotic replacement of malignant tissue - from residual disease. Restaging is typically performed with contrast-enhanced CT or MRI, which can evaluate changes in tumor characteristics as hypodensity; however, these modalities may overestimate residual disease, particularly at the lesion margins. Such limitations can lead to misinterpretation of treatment response, potentially resulting in unnecessary prolongation of chemotherapy and delays in proceeding to surgery with curative intent.

Serum biomarkers including CA19-9, may provide additional guidance when imaging findings are equivocal, but their decline is often variable and not always pronounced. Moreover, as indicated earlier, a subpopulation of patients does not express reliable tumor markers, further complicating the assessment.

In general, a favorable response to chemotherapy is suggested by the absence of newly detected metastases, stability or improvement in vascular involvement, and a meaningful decline in tumor marker levels when assessable. Nonetheless, the decision to proceed with surgical resection ultimately depends on the surgeon's evaluation of resectability.

Surgical procedures vary according to tumor location. Lesions involving the pancreatic head are typically managed with pancreaticoduodenectomy, either through the classic Whipple procedure or Traverso-Longmire reconstruction (pylorus-preserving pancreaticoduodenectomy - PPPD), combined with an appropriate lymphadenectomy. Tumors involving the pancreatic body (proximal to the gastroduodenal artery) or tail are usually treated with distal pancreatectomy and splenectomy, the latter being necessary to allow adequate removal of lymphatic tissue along the splenic artery.

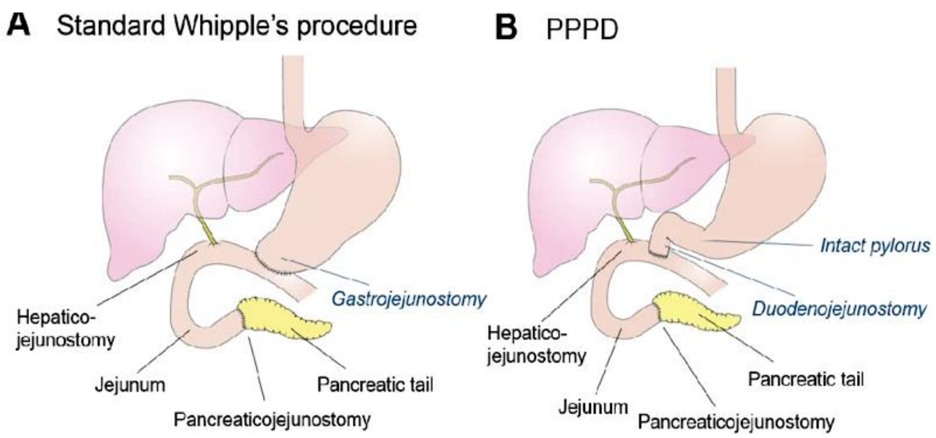


Figure 4 - Surgical techniques: standard Whipple procedure and pylorus-preserving pancreaticoduodenectomy (PPPD).

These procedures may be carried out via an open approach or through minimally invasive techniques, including laparoscopy and robotic surgery. The latter may offer technical advantages over conventional laparoscopy, particularly during delicate reconstructive steps such as the pancreatojejunostomy, due to their greater deftness and range of motion.

In specific cases more complex resections are necessary, as in tumor involvement of the celiac axis, that can be addressed with an Appleby procedure. Venous resections involving the portal or superior mesenteric vein can also be performed safely in specialized centers, with outcomes comparable to standard resections. In contrast, arterial reconstruction should be reserved for highly selected patients due to its significant morbidity and the need for management in high-volume, experienced institutions. Evidence suggests that, in carefully chosen cases, pancreatectomy with arterial resection may offer better outcomes than palliative treatment in borderline resectable or locally advanced disease. Additionally, multivisceral resections, although technically demanding, can be considered in fit patients when required to achieve complete tumor clearance.

2.6. Management and follow-up after surgery

Postoperative management is guided by pathological findings, margin status, nodal involvement, and preoperative treatment strategy.

In most cases, adjuvant chemotherapy is recommended, even for early-stage tumors without nodal involvement. For patients who have already undergone neoadjuvant therapy, completion of the planned systemic regimen is generally advised. The benefit of adjuvant treatment over observation alone was first demonstrated in the CONKO-001 trial, where Gemcitabine significantly improved overall survival (OS) compared with follow-up alone.

Several chemotherapy regimens are active in pancreatic cancer. Among these, modified FOLFIRINOX (mFOLFIRINOX) is currently the preferred option in the adjuvant setting, having demonstrated significant improvements in both disease-

free survival (DFS) and overall survival (OS) compared with Gemcitabine alone (PRODIGE 4 trial).
The combination of Gemcitabine and Nab-paclitaxel represents a valid alternative, particularly in patients who are not candidates for FOLFIRINOX or in those with disease recurrence or progression.

Treatment selection is strongly influenced by patient performance status (ECOG), as FOLFIRINOX is associated with significant toxicity and is generally reserved for fit individuals, whereas less intensive regimens or single-agent therapy are considered in more fragile patients.

After completion of adjuvant therapy, follow-up typically consists of regular clinical assessments, contrast-enhanced imaging of the chest, abdomen, and pelvis, and monitoring of CA19-9 levels every 3-6 months during the first two postoperative years, and at longer intervals thereafter.
Thus, the intensive surveillance may facilitate early detection of recurrence during follow-up, particularly in asymptomatic patients, and increases the likelihood of receiving additional treatment, associated with more favorable outcome.
For patients with limited functional status, palliative care and best supportive management should be considered as appropriate alternatives to further systemic treatment.

2.7. Recurrence, patterns of recurrence and site-specific management of PDAC after curative-intent resection

Despite curative-intent surgery, recurrence remains extremely common and occurs in up to 80% of patients, often within the first two years after resection.
Early recurrence, usually defined as relapse within 6 months after surgery, is associated with aggressive tumor biology and poor outcomes.
Recurrence patterns are biologically heterogeneous and include liver, lung, locoregional, peritoneal, and multi-site disease. Each pattern is associated with

distinct biological behavior and prognostic implications and may reflect underlying tumor biology.

Liver metastases represent the most frequent site of recurrence, occurring in approximately 30-50% of patients. This pattern is traditionally associated with poor survival outcomes, reflecting early hematogenous dissemination and systemic disease progression. However, emerging evidence suggests that, in highly selected patients, liver-directed strategies such as surgical resection or ablative approaches may provide meaningful survival benefit. The systematic review and meta-analysis demonstrate improved overall survival (OS) compared with systemic treatment alone (HR 0.26, 95% CI 0.14–0.49), with the strongest effect observed for surgical resection (HR 0.18, 95% CI 0.11–0.31).

Pulmonary recurrence, observed in approximately 10-20% of cases, is increasingly recognized as a distinct clinical phenotype. Compared with other metastatic patterns, lung-only recurrence is generally associated with a more indolent clinical course, later onset, and more favorable survival outcomes. In selected patients, median post-recurrence survival may exceed 15 months, particularly when surgical resection or stereotactic body radiotherapy (SBRT) is feasible.
Consistently, surgical resection of isolated lung metastases is associated with improved post-recurrence survival compared with non-surgical management (HR 0.35, 95% CI 0.26–0.48), supporting the hypothesis of organ-preferential metastatic behavior rather than uniform systemic dissemination.

Locoregional recurrence, involving the pancreatic bed, remnant pancreas, or regional lymphatic stations, occurs in approximately 20-30% of patients. This pattern is often technically challenging due to proximity to major vascular structures and the retroperitoneum. Median survival in this setting remains limited (approximately 5 months); however surgical resection has been associated with improved outcomes compared with non-surgical approaches (HR 0.52, 95% CI 0.38–0.72), although heterogeneity is considerable due to variability in surgical indications and technical feasibility. Stereotactic body radiotherapy (SBRT) has shown promising short-term disease control in small non-comparative series, but strong comparative evidence is still lacking.

Peritoneal dissemination and multi-site recurrence typically reflect diffuse systemic disease and are associated with the worst prognosis, often precluding the use of local therapeutic strategies and limiting management to systemic therapy or best supportive care.

Biochemical recurrence represents and additional clinical challenge, and it is observed in approximately 10–15% of patients as an isolated elevation in carbohydrate antigen 19-9 (CA19-9) without radiological evidence of disease.
Within the POCÉMON study framework, biochemical recurrence is defined as a confirmed and persistent rise in CA19-9 after an initial postoperative decline, documented on at least two separate measurements in the absence of radiological evidence of the disease. In this context, management remains non-standardized and typically guided by multidisciplinary evaluation.

The timing of recurrence is closely linked to underlying tumor biology: early relapse, particularly within 6-12 months, is typically associated with more aggressive disease and a higher likelihood of liver-dominant or multi-site recurrence, whereas later recurrence more frequently presents as isolated patterns, especially pulmonary metastases.

Management of recurrent pancreatic ductal adenocarcinoma (PDAC) remains highly complex and is characterized by substantial clinical heterogeneity. Despite advances in perioperative treatment, recurrence is the rule rather than the exception, and therapeutic strategies remain largely individualized.
Treatment decisions are typically formulated within multidisciplinary team (MDT) discussions guided by patient performance status (ECOG), recurrence pattern, disease burden, prior therapies, and time to relapse.

Systemic chemotherapy remains the cornerstone of treatment, with regimens such as modified FOLFIRINOX (mFOLFIRINOX) or Gemcitabine plus Nab-Paclitaxel selected according to prior exposure and patient tolerance. Nevertheless, the traditional view that recurrent PDAC represents a uniformly systemic condition is increasingly questioned, particularly in patients with isolated or oligometastatic relapse.

Growing evidence suggests a recurrence pattern-driven approach, suggesting the existence of biologically and clinically distinct subgroups that may benefit from site-adapted therapeutic strategies. This concept of a "site-specific therapeutic window" implies that the selected patients with limited disease burden may achieve improved outcomes with aggressive local therapies.

The increasing use of neoadjuvant chemotherapy has further modified recurrence dynamics, with emerging evidence data suggesting delayed relapse and a relative increase in pulmonary metastases compared with liver-dominant recurrence. Whether this reflects true biological modulation or treatment-related selection remains unresolved, but it has important implications for post-recurrence management.

Given the variability in recurrence patterns and therapeutic approaches, prospective standardization is urgently needed. The present study aims to address this gap by systematically characterizing recurrence timing, distribution, and management strategies in a large multicenter cohort, integrating radiological and biochemical definitions with post-recurrence treatment strategies and survival outcomes.

This approach will enable comparison between neoadjuvant-treated and upfront surgery cohorts, facilitate identification of predictors of early recurrence, and improve selection criteria for aggressive post-recurrence interventions. Ultimately, this may contribute to more accurate prognostic stratification and a more rational, biology-informed management of recurrent PDAC.

3. Aim of the study

The present study aims to investigate recurrence patterns and their management following curative-intent resection for pancreatic ductal adenocarcinoma (PDAC) within the framework of the POCÉMON project.

Given the high incidence of postoperative relapse, particularly within the first two years, the analysis focuses on characterizing recurrence according to anatomical site (local, liver, lung, peritoneal, multiple sites), timing, and mode of detection (radiologic versus biochemical).

Specific focus is also dedicated to biochemical recurrence, defined as isolated CA19-9 elevation in the absence of radiologic evidence of disease, with analysis of its detection and management in clinical practice.

A second objective is to describe the clinical characteristics of different recurrence patterns and the treatments adopted in routine practice. Recurrence after PDAC resection is heterogeneous, with distinct clinical behaviors across patterns. In this context, the study will analyze post-recurrence treatments, including systemic chemotherapy, surgical resection, ablative procedures, and stereotactic body radiotherapy, to assess how recurrence patterns influence therapeutic choices.

Additionally, the study aims to compare treatment strategies and survival outcomes across recurrence scenarios, especially considering factors associated with improved prognosis, such as disease-free interval, recurrence burden, prior treatments, and biological behavior.

Comparisons between patients treated with neoadjuvant therapy and those undergoing upfront surgery will also be performed to explore differences in recurrence dynamics and subsequent management.

Overall, the study seeks to refine patient selection for multimodal treatment approaches and contribute to a more evidence-based and individualized management of recurrent PDAC.

4. Materials and methods

This study was designed as a retrospective multicenter observational cohort analysis conducted in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

Data were collected from prospectively maintained or retrospectively reviewed institutional databases of high-volume pancreatic cancer centers with dedicated multidisciplinary expertise in pancreatic cancer management. The study period included patients treated between January 2015 and December 2023, ensuring adequate follow-up for recurrence assessment.

As an observational study, diagnostic and therapeutic decisions were left to institutional practice, allowing assessment of recurrence patterns and management across centers.

Eligible patients were adults (≥ 18 years) who underwent curative-intent resection (R0 or R1) for histologically confirmed pancreatic ductal adenocarcinoma, with no evidence of distant metastasis at the time of surgery and a minimum follow-up of 18 months, unless recurrence or death occurred earlier.

Exclusion criteria included R2 or palliative resections, intraoperative detection of metastatic or unresectable disease, non-PDAC histology, incomplete follow-up data, and perioperative mortality within 90 days from surgery.

Preoperative resectability assessment was performed by institutional multidisciplinary teams (MDTs) according to established international criteria, including the National Comprehensive Cancer Network (NCCN) guidelines.

Tumor staging and resectability evaluation were based on high-quality imaging (contrast-enhanced CT or MRI) together with CA19-9 assessment. Patients were stratified according to initial treatment strategy into neoadjuvant therapy and upfront surgery groups.

Perioperative management included neoadjuvant therapy, consisted of modern chemotherapy regimens as FOLFIRINOX or Gemcitabine-based protocols, with or without radiotherapy. Surgical procedures included pancreaticoduodenectomy, distal pancreatectomy, or total pancreatectomy, with or without vascular or multivisceral resections - performed when necessary to achieve complete tumor removal - and adjuvant chemotherapy.

Postoperative surveillance and follow-up consisted of regular clinical evaluation, cross-sectional imaging every three months during the first two years, and serial CA19-9 measurements.

Recurrence was categorized by anatomical site (local, liver, lung, peritoneal, or multiple-site), timing, and mode of detection (radiologic or biochemical).

Biochemical recurrence was defined as a persistent and confirmed increase in CA19-9 levels after an initial postoperative decline in the absence of radiological evidence of disease.

Inclusion criteria	Exclusion criteria
• Histologically confirmed **PDAC** • **Curative-intent** surgical resection • **No distant metastasis** at the time of surgery • A minimum follow-up of **18 months** (unless recurrence/ death within 18 months) • Availability of baseline imaging and tumor marker data (preop CA19-9 and pancreas-protocol CT or MRI)	• Age <18 years • R2 resection, palliative or diagnostic surgeries • Intraoperative discovery of distant metastasis or unresectable disease • Non-PDAC histology • Incomplete clinical or radiologic follow-up precluding recurrence assessment • Mortality within 90 days of surgery

Table II - Inclusion and exclusion criteria of the study

Post-recurrence treatment strategies were recorded in detail and included systemic chemotherapy, surgical resection, radiotherapy (including stereotactic body radiotherapy), or best supportive care. Treatment intent was classified as curative or palliative according to institutional multidisciplinary evaluation.

Data were collected using standardized case report forms and recorded into a centralized, anonymized multicenter database. Variables included patient demographics, tumor characteristics (stage, grade, nodal status, margin status), treatment details (neoadjuvant, surgical, and adjuvant therapies), postoperative outcomes, follow-up data, and recurrence characteristics. Recurrence was defined as radiologic, histologic, or unequivocal biochemical evidence of disease after a disease-free interval.

Survival endpoints included overall survival (OS), recurrence-free survival (RFS), and post-recurrence survival (PRS). Data quality was ensured through local investigator supervision, standardized definitions, and periodic consistency checks.

Descriptive statistics were used to summarize baseline characteristics, recurrence patterns, and treatment strategies.

Time-to-event outcomes (OS, RFS, and PRS) were estimated using the Kaplan–Meier method and compared with the log-rank test. Cox proportional hazards regression models were applied to identify factors associated with survival outcomes, and results were reported as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Multivariable analyses adjusted for potential confounders, including patient characteristics, tumor features, treatment variables, and recurrence patterns. Subgroup analyses were conducted according to recurrence site, treatment modality, and initial treatment strategy (neoadjuvant versus upfront surgery).

A p-value <0.05 was considered statistically significant. Statistical analyses were performed using validated software packages.

5. Results

5.1. Study population

A total of 1176 patients who underwent curative-intent resection for pancreatic ductal adenocarcinoma (PDAC) between 2015 and 2023 at the participating institutions were included in the preliminary POCÉMON Red cohort analysis. Among them, 712 patients (60.5%) developed recurrence during follow-up, whereas 464 patients (39.5%) remained recurrence-free.

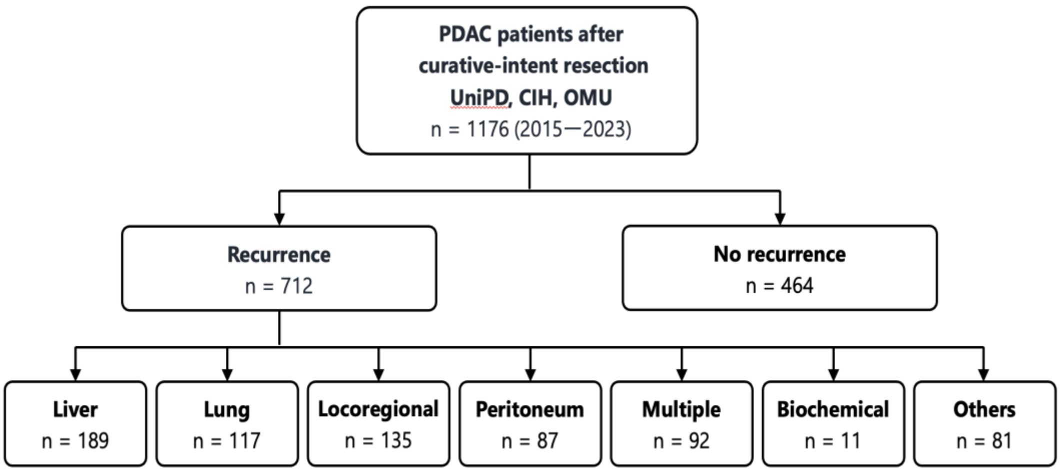


Figure 5 - Distribution of recurrence patterns in patients with PDAC after curative-intent resection (2015 – 2023)

The median age of patients who developed recurrence was 70 years (IQR 63–75), and 53.2% were male. Most patients presented with anatomically resectable disease at diagnosis (62.7%), while 30.1% had borderline resectable disease and 7.0% had locally advanced disease. Neoadjuvant treatment had been administered in 50.2% of patients, and adjuvant chemotherapy was delivered in 81.5%.

	Total (n = 712)
Age, median (IQR), years	70.0 (63.0–75.0)
Male sex, n (%)	386 (53.2)
Anatomical resectability, n (%)	
Resectable	447 (62.7)
Borderline resectable	214 (30.1)
Locally advanced	50 (7.0)
Neoadjuvant treatment, n (%)	358 (50.2)
Surgical procedure, n (%)	
Pancreatoduodenectomy	454 (63.8)
Left pancreatectomy	238 (33.4)
Total pancreatectomy	20 (2.8)
Vascular resection, n (%)	331 (46.5)
Clavien–Dindo grade ≥IIIa, n (%)	135 (19.0)
Length of hospital stay, median (IQR), days	19.0 (15.0–30.0)
Adjuvant chemotherapy, n (%)	580 (81.5)
pN1–2, n (%)	449 (63.1)
R0 status, n (%)	389 (54.6)
Predominant site of recurrence, n (%)	
Liver	189 (26.5)
Lung	117 (16.4)
Local	135 (19.0)
Peritoneum	87 (12.2)
Multiple	92 (12.9)
Biochemical	11 (1.5)
Others	81 (11.4)
Early recurrence, n (%)	175 (24.6)

Table III - Baseline characteristics of the study population with recurrent PDAC (n = 712)

5.2. Recurrence patterns

Among recurrent cases, liver recurrence represented the most frequent pattern (n = 189, 26.5%), followed by locoregional recurrence (n = 135, 19.0%), lung recurrence (n = 117, 16.4%), multiple-site recurrence (n = 92, 12.9%), peritoneal recurrence (n = 87, 12.2%), and other recurrence patterns (n = 81, 11.4%). Biochemical-only recurrence was uncommon and observed in 11 patients (1.5%).

	Liver (n=189)	Lung (n=117)	Locoregional (n=135)	Peritoneum (n=87)	Multiple (n=92)	Others (n=81)
Age, median (IQR), years	69.0 (63.0–75.0)	71.0 (64.0–75.0)	70.0 (62.0–76.5)	71.0 (62.5–77.0)	70.0 (63.5–75.0)	69.0 (65.0–73.0)
Male sex, n (%)	108 (57.1)	55 (47.0)	70 (51.9)	51 (58.6)	50 (54.3)	47 (58.0)
Anatomical resectability, n (%)						
Resectable	123 (65.1)	68 (58.1)	83 (61.9)	58 (66.7)	57 (62.0)	50 (61.7)
Borderline resectable	55 (29.1)	42 (35.9)	42 (31.3)	20 (23.0)	29 (31.5)	24 (29.6)
Locally advanced	11 (5.8)	7 (6.0)	9 (6.7)	9 (10.3)	6 (6.5)	7 (8.6)
Neoadjuvant treatment, n (%)	79 (41.8)	73 (62.4)	52 (38.5)	54 (62.1)	56 (60.9)	41 (50.6)
Surgical procedure, n (%)						
Pancreatoduodenectomy	128 (67.7)	76 (65.0)	92 (68.1)	36 (41.4)	62 (67.4)	53 (65.4)
Left pancreatectomy	54 (28.6)	39 (33.3)	42 (31.1)	47 (54.0)	28 (30.4)	25 (30.9)
Total pancreatectomy	7 (3.7)	2 (1.7)	1 (0.7)	4 (4.6)	2 (2.2)	3 (3.7)
Vascular resection, n (%)	85 (45.0)	48 (41.4)	69 (51.1)	39 (44.8)	50 (54.3)	33 (40.7)
Clavien–Dindo grade ≥IIIa, n (%)	40 (21.2)	25 (21.6)	20 (14.8)	27 (31.0)	13 (14.1)	9 (11.1)
Length of hospital stay, median (IQR), days	19.0 (14.0–31.0)	21.0 (16.0–29.3)	19.0 (14.0–30.0)	20.0 (13.5–30.0)	20.0 (16.0–31.0)	18.0 (15.0–27.0)
Adjuvant chemotherapy, n (%)	141 (74.6)	94 (80.3)	115 (85.2)	77 (88.5)	78 (84.8)	66 (81.5)
pN1–2, n (%)	122 (64.9)	70 (60.3)	86 (63.7)	52 (60.5)	66 (71.7)	45 (55.6)
R0 status, n (%)	105 (74.5)	64 (74.4)	77 (68.1)	55 (77.5)	30 (62.5)	54 (83.1)
Early recurrence, n (%)	85 (45.0)	14 (12.0)	17 (12.6)	25 (28.7)	17 (18.5)	14 (17.3)

Table IV - Baseline characteristics of the study population with recurrent PDAC by recurrence pattern

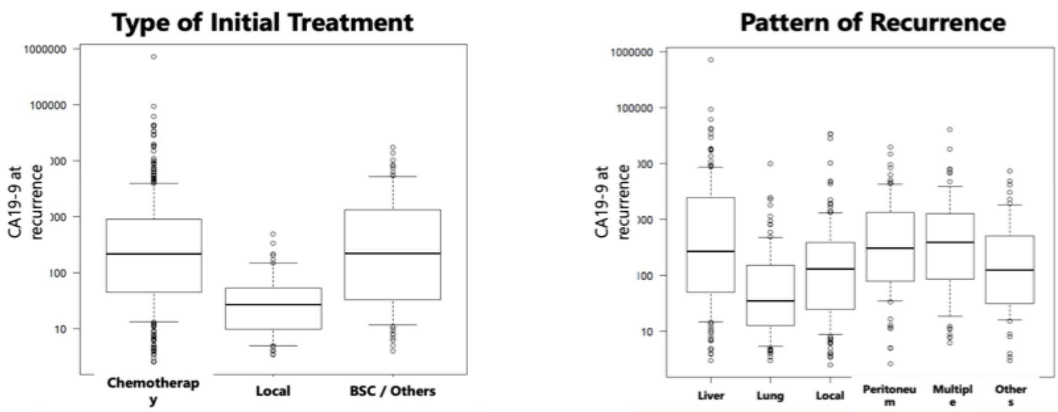
Substantial differences emerged across recurrence patterns regarding recurrence timing and disease behavior. Lung recurrence was associated with the longest recurrence-free interval (median 569 days), whereas liver recurrence showed the shortest interval (median 198 days), suggesting a more aggressive biological behavior. Early recurrence was most frequent in liver recurrence (45.0%) and less common in lung (12.0%) and locoregional recurrence (12.6%).

5.3. Detection methods

Biochemical-only recurrence was rare and observed in 11 patients (1.5%) and represented a challenging clinical scenario due to the absence of radiological evidence of disease despite persistent tumor marker elevation.

CA19-9 levels at recurrence differed significantly according to recurrence pattern and treatment strategy. Lung recurrence showed the lowest median CA19-9 levels (34.5 U/mL), whereas multiple-site and peritoneal recurrence showed the highest levels (388.8 U/mL and 304.3 U/mL, respectively).

Patients selected for local therapy generally showed lower median CA19-9 levels at recurrence (26.6 U/mL) compared with those managed with systemic chemotherapy (216.3 U/mL) or best supportive care (218.6 U/mL) ($P < 0.001$), suggesting a strong association between tumor burden, biological behavior, and treatment allocation.



Treatment	Median CA19-9 (U/mL)
Chemotherapy	216.3
Local	26.6
BSC / Others	218.6

Recurrence site	Median CA19-9 (U/mL)
Liver	265.8
Lung	34.5
Locoregional	128.5
Peritoneum	304.3
Multiple	388.8

Figure 6 - CA19-9 levels at initial recurrence

5.4. Treatment strategies

Systemic therapy represented the predominant first-line treatment strategy across all recurrence patterns. However, the use of local treatment strategies varied considerably according to recurrence site.

Local treatment was most frequently adopted in patients with lung recurrence, where 29.1% underwent local treatment as the initial strategy, compared with 17.0% in locoregional recurrence and only 1.1% in liver recurrence. In contrast, peritoneal and multiple-site recurrences were almost exclusively managed with systemic therapy or best supportive care.

Metastasectomy during the disease course was markedly more common in lung recurrence (32.5%) compared with liver recurrence (3.2%) or peritoneal recurrence (3.4%), reflecting the more indolent nature and potentially favorable biology of isolated pulmonary metastases.

These findings suggest that both recurrence site and tumor marker burden strongly influenced post-recurrence treatment selection.

Variable	Liver (n=189)	Lung (n=117)	Locoregional (n=135)	Peritoneum (n=87)	Multiple (n=92)	Others (n=81)
Recurrence-free interval, median (IQR), days	198.0 (113.0–356.0)	569.0 (321.0–882.0)	412.0 (14.0–648.0)	366.0 (163.5–555.5)	347.0 (224.0–661.0)	379.0 (239.0–662.0)
Initial recurrence treatment, n (%)						
Systemic therapy	146 (77.2)	76 (65.0)	97 (71.9)	69 (79.3)	77 (83.7)	68 (84.0)
Local therapy	2 (1.1)	34 (29.1)	23 (17.0)	1 (1.1)	0 (0.0)	2 (2.5)
BSC / Others	41 (21.7)	7 (6.0)	15 (11.1)	17 (19.5)	15 (16.3)	11 (13.6)
2nd line therapy, n (%)						
Systemic therapy	82 (91.1)	62 (86.1)	66 (85.2)	31 (88.6)	41 (84.8)	34 (79.1)
Local therapy	6 (6.6)	9 (12.5)	9 (11.9)	3 (8.6)	5 (10.8)	9 (21.0)
Others	2 (4.4)	1 (1.4)	1 (1.3)	1 (2.9)	0 (0.0)	3 (0.0)
Any metastasectomy during disease course, n (%)	6 (3.2)	38 (32.5)	15 (11.1)	3 (3.4)	3 (3.3)	7 (8.6)

Table V - Recurrence Treatment Details

5.5. Survival outcomes

Marked differences in survival outcomes were observed according to recurrence pattern.

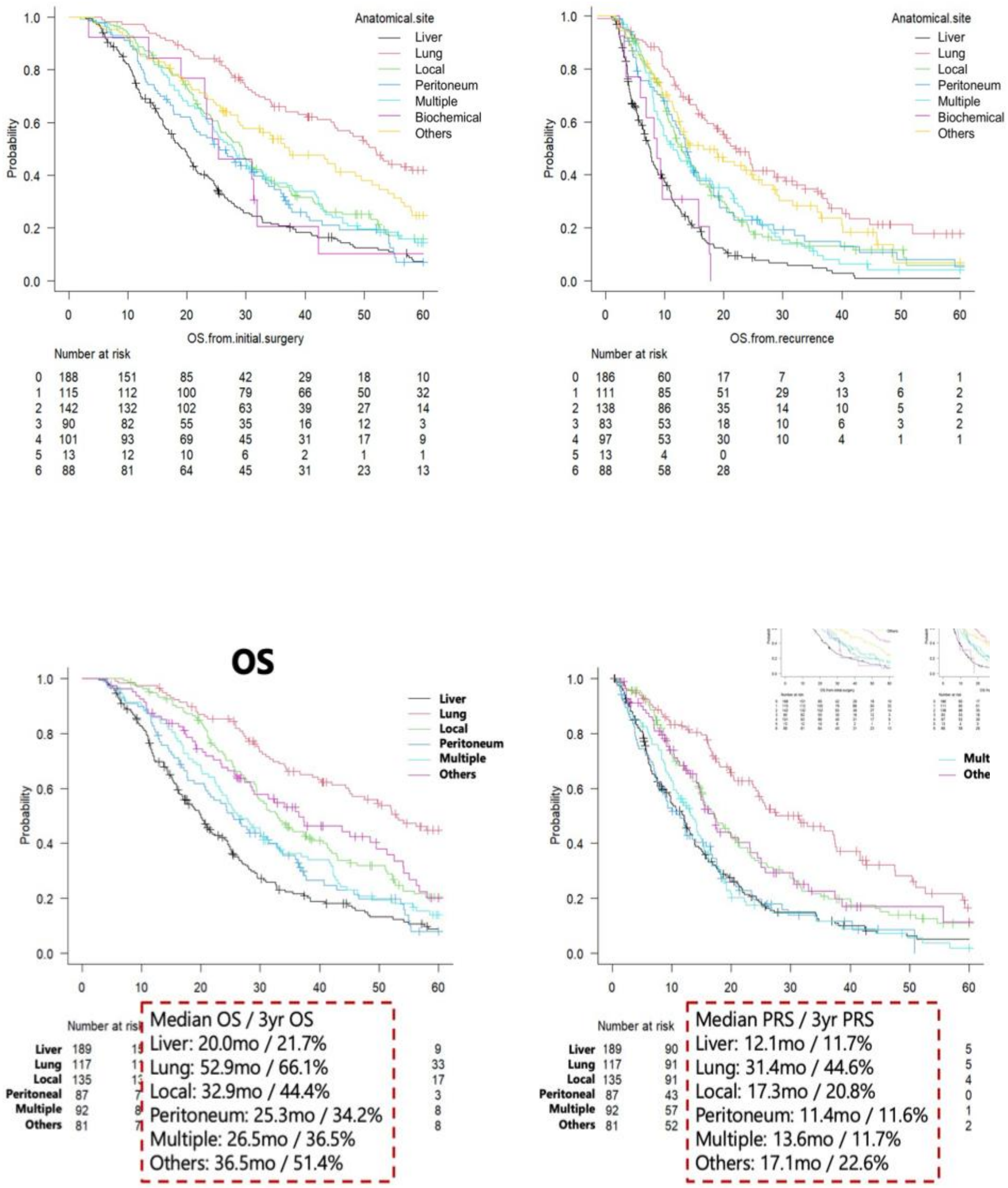


Figure 7 - Survival Stratified by Recurrence-site

Liver recurrence was associated with the poorest prognosis among single-site recurrences, with a median overall survival (OS) of 20.0 months and a median post-recurrence survival (PRS) of 12.1 months. In contrast, patients with lung recurrence demonstrated the most favorable outcomes, with a median OS of 52.9 months and a median PRS of 31.4 months.

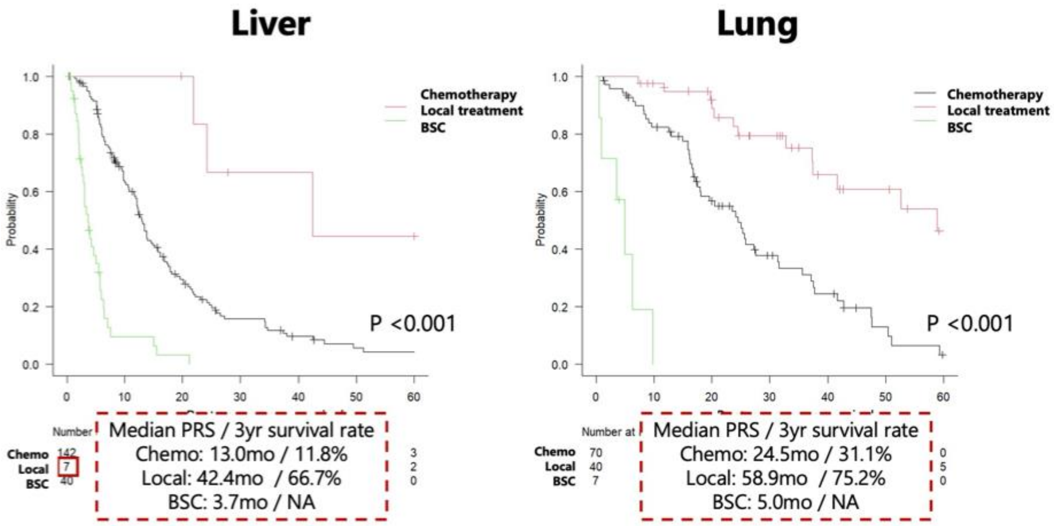


Figure 8 - Post-recurrence Survival in liver and lung metastases

Locoregional recurrence showed intermediate outcomes, with a median OS of 32.9 months and a median PRS of 17.3 months. Peritoneal and multiple-site recurrences were associated with poor survival, with median PRS values of 11.4 and 13.6 months, respectively.

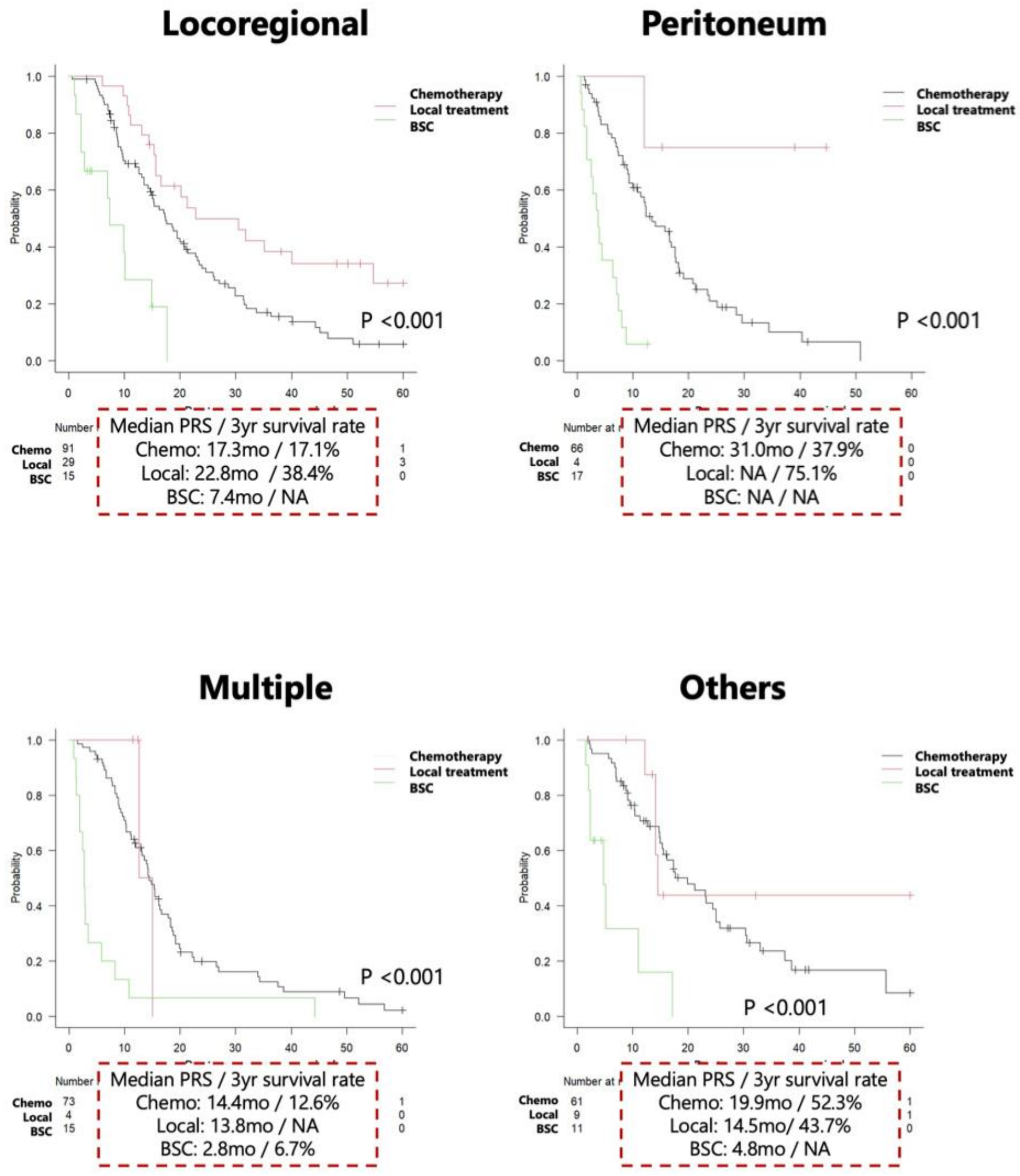


Figure 9 - Post-recurrence Survival in locoregional, peritoneal, multiple and other metastases

Kaplan–Meier analyses demonstrated significant survival differences between recurrence patterns for both OS and PRS (P < 0.001).

5.6. Treatment impact

Within each recurrence pattern, patients treated with local therapeutic approaches consistently demonstrated superior survival outcomes compared with patients receiving chemotherapy alone or best supportive care.

The survival advantage associated with local treatment was particularly evident in patients with pulmonary recurrence. Patients receiving surgery or stereotactic radiotherapy achieved prolonged post-recurrence survival and, in some cases, exceptionally long overall survival. Specifically, median post-recurrence survival (PRS) was 58.9 months, with a 3-year PRS rate of 75.2%, compared with 24.5 months and 31.1% respectively, among patients treated with chemotherapy alone ($P < 0.001$). In selected patients receiving local treatment, median overall survival exceeded 100 months.
A similar, although less pronounced, trend was also observed in patients with locoregional and liver recurrence.

In patients with liver recurrence, local therapy was associated with a median post-recurrence survival (PRS) of 42.4 months, compared with 13.0 months in those receiving chemotherapy and 3.7 months in patients managed with best supportive care ($P < 0.001$). Median overall survival (OS) reached 63.0 months in the local treatment group versus 20.6 months with chemotherapy alone.

Likewise, in locoregional recurrence, local therapy was associated with improved survival compared with systemic treatment alone, although the significance of benefit appeared less marked than that observed in pulmonary recurrence. However, multivariable analyses suggested that these favorable outcomes were strongly influenced by patient selection and underlying tumor biology rather than by treatment effect alone.

In contrast, patients with peritoneal or multiple-site recurrence rarely underwent local treatment, likely reflecting the disseminated nature and more aggressive biology of disease in these settings.

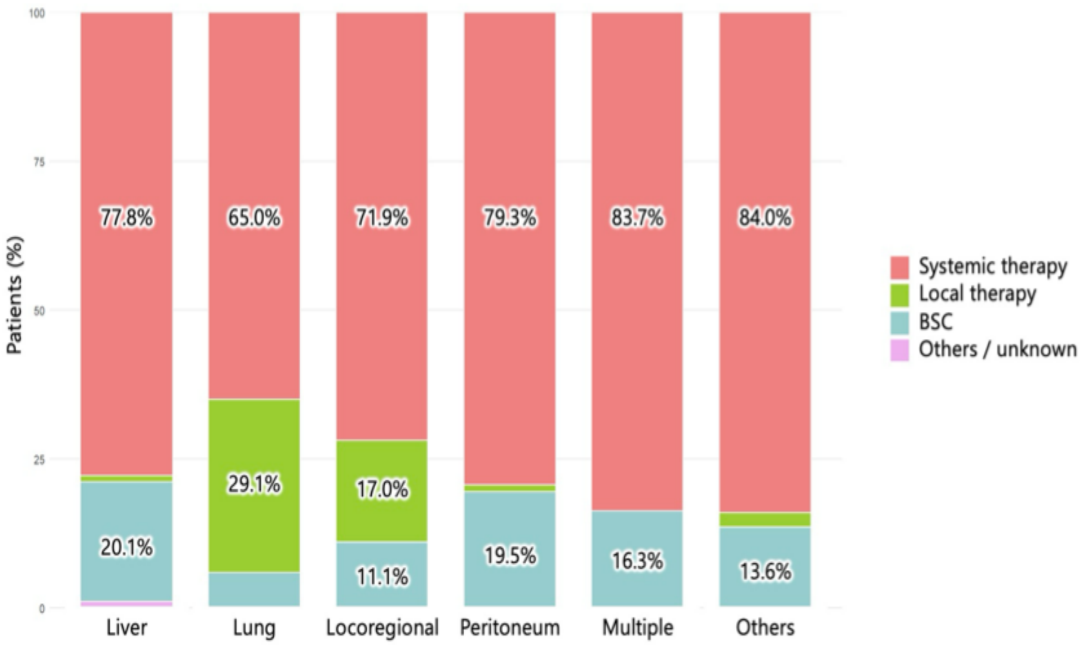


Figure 10 - Initial Treatment Strategy by Recurrence Pattern

5.7. Prognostic factors

Multivariable Cox regression analysis identified several independent prognostic factors associated with post-recurrence survival (PRS).

Increasing age (HR 1.024, 95% CI 1.014–1.034, P < 0.001), nodal positivity (pN1–2) (HR 1.219, 95% CI 1.012–1.469, P = 0.037), and elevated CA19-9 levels at recurrence (HR 1.287, 95% CI 1.173–1.412, P < 0.001) were independently associated with worse outcomes. Conversely, a longer recurrence-free interval was associated with improved outcomes (HR 0.9989, 95% CI 0.9986–0.9992, P < 0.001), and pulmonary recurrence was independently associated with more favorable survival compared with liver recurrence (HR 0.597, 95% CI 0.436–0.819, P = 0.001).

Although local treatment strategies showed a strong association with improved survival in univariable analysis (HR 0.332, 95% CI 0.230–0.481, P < 0.001), this association lost statistical significance after multivariable adjustment (HR 0.720, 95% CI 0.481–1.077, P = 0.110), suggesting that the apparent survival benefit was largely influenced by treatment selection and underlying biological and clinical factors rather than by treatment effect alone.

	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Age, per year	1.025	1.015–1.034	**<0.001**	1.024	1.014–1.034	**<0.001**
Male sex	1.134	0.957–1.344	0.146	—	—	—
pN1–2	1.289	1.080–1.540	**0.005**	1.219	1.012–1.469	**0.037**
Log_{10}CA19-9 at recurrence	1.412	1.295–1.539	**<0.001**	1.287	1.173–1.412	**<0.001**
Recurrence-free interval, per day	0.9987	0.9984–0.9990	**<0.001**	0.9989	0.9986–0.9992	**<0.001**
Local treatment post-rec.	0.332	0.230–0.481	**<0.001**	0.720	0.481–1.077	0.110
Recurrence site						
Liver	Ref.	—	—	Ref.	—	—
Lung	0.388	0.293–0.514	**<0.001**	0.597	0.436–0.819	**0.001**
Locoregional	0.632	0.492–0.810	**<0.001**	0.868	0.666–1.132	0.296
Peritoneum	1.041	0.785–1.382	0.779	1.116	0.827–1.506	0.474
	0.977	0.747–1.279	0.866	1.080	0.814–1.432	0.595
						0.297

Table VI - Cox-regression Analysis for Post-recurrence Survival

6. Discussion

6.1. Main findings

The present multicenter study demonstrates that recurrence after curative-intent resection for pancreatic ductal adenocarcinoma (PDAC) is characterized by substantial biological and clinical heterogeneity.

Recurrence patterns differed substantially in terms of timing, tumor marker burden, treatment allocation, and survival outcomes, highlighting the concept that recurrent PDAC should not be considered a single clinical entity.

Among the analyzed recurrence patterns, pulmonary recurrence emerged as a clinically distinct entity, with the most favorable phenotype.
These patients were characterized by longer recurrence-free intervals, lower CA19-9 levels at relapse, more frequent use of local treatment strategies, and significantly prolonged post-recurrence survival compared with other recurrence types.

In contrast, liver recurrence was associated with earlier relapse, higher tumor marker levels, and markedly worse survival outcomes, reflecting a more aggressive biological behavior.

Peritoneal and multiple-site recurrences similarly demonstrated poor prognosis and limited therapeutic options, whereas locoregional recurrence represented an intermediate clinical scenario characterized by substantial heterogeneity and highly individualized management strategies.

6.2. Interpretation

The marked differences observed across recurrence sites likely reflect distinct biological behaviors and metastatic mechanisms.

Liver recurrence appears to represent a rapidly progressive systemic disease phenotype characterized by early hematogenous dissemination. The high incidence of early relapse and elevated CA19-9 levels observed in these patients further support the hypothesis of aggressive tumor biology already present at the time of surgery, despite apparently curative resection.

Conversely, pulmonary recurrence may represent a more indolent metastatic phenotype. The longer disease-free interval, lower tumor marker burden, and prolonged survival observed in this subgroup are consistent with previous evidence suggesting a slower metastatic progression and a potentially more favorable tumor biology. This may partly explain why selected patients with isolated lung metastases appear to derive greater benefit from local therapeutic strategies such as metastasectomy or stereotactic radiotherapy.

Locoregional recurrence showed intermediate characteristics, reflecting the complexity of distinguishing persistent microscopic disease from true metastatic progression. Management of these patients remains technically demanding due to previous surgery, retroperitoneal fibrosis, and proximity to major vascular structures.

6.3. Role of local therapies

One of the most clinically relevant findings of the present study concerns the potential role of local treatment strategies in carefully selected patients with recurrent PDAC.

Patients treated with surgery, ablative procedures, or stereotactic body radiotherapy (SBRT) consistently demonstrated improved survival compared with those receiving systemic therapy alone, particularly in the setting of isolated pulmonary recurrence and, to a lesser extent, liver and locoregional metastases. In some patients, survival outcomes appeared remarkably prolonged, suggesting the existence of a subgroup with more favorable tumor biology and limited metastatic potential.

However, the survival benefit associated with local treatment lost statistical significance after multivariable adjustment. This finding strongly suggests that treatment allocation itself is heavily influenced by underlying biological selection factors, including lower disease burden, lower CA19-9 levels, longer recurrence-free interval, and better patient performance status.

Therefore, local therapies should not be interpreted as universally beneficial in recurrent PDAC but rather as part of a highly individualized and multidisciplinary treatment strategy applicable only to carefully selected patients.

6.4. Literature comparison

The present findings align with the growing body of literature suggesting that relapse after PDAC resection is biologically heterogeneous and that recurrence site significantly influences prognosis.
Several previous studies have demonstrated improved survival associated with local treatment in selected patients with liver-only, lung-only, and locoregional recurrence, supporting the concept of organ-specific metastatic behavior.

Together, these analyses reinforce the concept that recurrence after PDAC resection should not be managed as a single biological entity.

6.5. Clinical implications

From a clinical perspective, these results reinforce the need for a more biology-oriented and recurrence-pattern-specific approach to recurrent PDAC.

Treatment decisions should not rely only on the presence or absence of recurrence but should integrate multiple clinical and biological factors, including recurrence site, recurrence-free interval, CA19-9 dynamics, disease extent, previous therapies and patient performance status.

The study also highlights the importance of multidisciplinary discussion in post-recurrence management. Selected patients with isolated or oligometastatic recurrence may benefit from aggressive local treatment approaches within experienced high-volume centers, whereas patients with rapidly progressive or disseminated disease are more likely to require systemic therapy or supportive care.

The increasing adoption of neoadjuvant therapy may further modify recurrence biology and recurrence distribution in the future, emphasizing the importance of continuous reassessment of recurrence patterns and treatment strategies.

6.6. Limitations

Several limitations should be acknowledged. First, the retrospective design inevitably introduces potential selection bias and confounding factors, particularly regarding the identification of true tumor biology, treatment allocation and the limited effective systemic treatment options.

Second, treatment protocols and follow-up strategies varied across participating centers and evolved over time, reflecting clinical heterogeneity.

Third, although this represents a large analysis focused on recurrence patterns after PDAC resection, certain recurrence subgroups — particularly biochemical recurrence — remained relatively small and may limit the reliability of subgroup analyses.

Finally, molecular and genomic data were not systematically available and therefore could not be integrated into the present analysis, despite their potentially important role in explaining differences in metastatic behavior and treatment response.

6.7. Future perspectives

Despite these limitations, the present study provides important insights into the biological heterogeneity of recurrent PDAC and post-recurrence treatment strategies after resection.

The multicenter international design and integration within the broader POCÉMON project provide a robust foundation for future prospective validation.

Future prospective studies are needed to validate recurrence-pattern-specific treatment strategies and to better define selection criteria for aggressive local therapies. The integration of molecular profiling, radiomics, biomarker analysis and liquid biopsy approaches may further improve prognostic stratification, enable earlier detection of recurrence, and help identify patients most likely to benefit from multimodal treatment approaches.

In parallel, ongoing advances in systemic therapy are expected to further expand the therapeutic landscape for recurrent PDAC. Emerging targeted therapies, including KRAS inhibitors, as well as immunotherapy-based strategies such as cancer vaccines and other immune-modulating approaches, may offer new opportunities for personalized treatment in selected patient subgroups.

A deeper understanding of the biological mechanisms underlying different recurrence phenotypes could ultimately contribute to the development of more personalized therapeutic algorithms and improved long-term outcomes for patients with recurrent PDAC.

7. Conclusions

This multicenter study demonstrates that recurrence after curative-intent resection for pancreatic ductal adenocarcinoma (PDAC) is characterized by significant biological and prognostic heterogeneity according to recurrence pattern.
Recurrence site was strongly associated with differences in recurrence timing, tumor marker burden, treatment allocation and survival outcomes, supporting the concept that recurrent PDAC should not be considered as a single clinical entity.

Among the analyzed recurrence patterns, pulmonary relapse appears to represent the most favorable phenotype, characterized by longer recurrence-free intervals, lower CA19-9 levels at recurrence, greater applicability of local treatment strategies and significantly prolonged post-recurrence survival.
In contrast, liver recurrence was associated with earlier relapse, higher tumor marker levels and markedly poorer survival outcomes, reflecting a more aggressive biological behavior.
Peritoneal and multiple-site recurrences similarly demonstrated poorer prognosis and limited eligibility for local therapeutic approaches, whereas locoregional recurrence represented a heterogeneous clinical scenario requiring individualized multidisciplinary evaluation.

The present study also highlights the potential role of aggressive local therapies in carefully selected patients with recurrent disease. Surgical resection, stereotactic body radiotherapy (SBRT) and other local approaches were associated with improved survival outcomes in selected recurrence patterns, particularly in patients with pulmonary recurrence. However, the absence of independent significance after multivariable adjustment suggests that favorable tumor biology and appropriate patients selection remain fundamental determinants of prognosis.

These findings support the adoption of a more personalized and biology-oriented approach to recurrent PDAC. The integration of recurrence pattern, recurrence-free interval, CA19-9 dynamics, disease extent, and patient performance status appears essential for optimizing therapeutic decision-making and refining patient selection for multimodal treatment strategies.
Although systemic chemotherapy remains the cornerstone of treatment for most patients, selected local therapies may represent a valuable component of a multidisciplinary treatment strategy in highly selected clinical scenarios.

Despite the inherent limitations of retrospective analyses, this study represents one of the largest contemporary multicenter investigations specifically focused on recurrence patterns and post-recurrence management after PDAC resection. Its integration within the broader POCÉMON project further strengthens the relevance of the findings and provides a solid foundation for future prospective validation studies.

Future research should aim to standardize recurrence-pattern-specific treatment algorithms, improve selection criteria for local therapies, and integrate molecular and biological profiling into clinical decision-making. A deeper understanding of recurrence biology may ultimately contribute to the development of more effective and individualized treatment strategies for patients with recurrent PDAC.

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