REVIEW

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LET'S NOT FORGET THAT THERE IS A PANCREAS IN THE ABDOMEN – A LITERATURE REVIEW ON PANCREATIC CANCER

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Abstract. *Globally, pancreatic cancer continues to be a significant health problem. The number of new cases has been increasing by an average of 0.8% per year over the last decade. The prognosis remains extremely poor, with a five-year survival rate of 7.2%, confirming its reputation as one of the deadliest malignant diseases.* ***Objective:*** *to analyze recent developments in the management of the diagnostic and treatment process for pancreatic cancer.* ***Materials and Methods:*** *systematic review of scientific publications through documentary analysis and analysis of the content of scientific publications selected by predefined key words.* ***Results and Discussion:*** *pancreatic cancer is one of the greatest clinical challenges in modern oncology, characterized by an extremely high mortality rate. Due to the lack of specific early manifestations and the biological aggressiveness of the disease, diagnosis is delayed in more than 80% of cases. Pancreatic disease should always be considered in the differential diagnosis of any acute or chronic pain. Successful management of these complex tumors requires a nuanced, multidisciplinary approach that integrates precise diagnosis, staging, and individualized therapeutic strategies.*

Key words: *pancreatic cancer, types of pancreatic cancer, staging, surgical treatment, targeted therapies*

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INTRODUCTION

Pancreatic cancer is one of the greatest clinical challenges in modern oncology, characterized by an extremely high mortality rate. This is largely due to its inherent biological aggressiveness and the difficulties in early diagnosis, which often lead to the disease being detected at an advanced stage. Successful management of these complex tumors requires a nuanced, multidisciplinary approach that integrates precise diagnosis, staging, and individualized therapeutic strategies. Pancreatic cancer encompasses a heterogeneous group of malignant neoplasms originating from the cells of the pancreas. The most common and aggressive form is pancreatic ductal adenocarcinoma (PDAC), which originates from the exocrine ductal cells. PDAC is the third most common cause of cancer-related death, with an extremely poor prognosis. Understanding the epidemiology of pancreatic cancer is of strategic importance, as trends in incidence and mortality, together with patterns of spread by histology and localization, inform public health strategies and guide clinical suspicion. Analysis of these data is key to identifying risk groups and highlights the urgent need for improved methods of early diagnosis. Globally, pancreatic cancer continues to be a significant health problem. The number of new cases has been increasing by an average of 0.8% per year over the last decade [1]. The prognosis remains extremely poor, with a five-year survival rate of 7.2%, confirming its reputation as one of the deadliest malignant diseases. **Objective:** this review aims to provide a detailed overview of the pathology, molecular characteristics, and current approaches to the treatment of malignant neoplasms of the pancreas. **Materials and methods:** systematic review of scientific publications through documentary analysis and content analysis of scientific publications selected by predefined key words.

Results: the fundamental distinction in pancreatic tumors is between exocrine and endocrine neoplasms, reflecting their cellular origin and biological behavior. The 2010 World Health Organization (WHO) classification provides a detailed histological framework that is essential for determining prognosis and treatment (Table 1).

Table 1. Classification of pancreatic tumors (WHO, 2010)

Category	Specific neoplasm
Benign	Acinar cell cystadenoma
	Serous cystadenoma
Premalignant lesions	Pancreatic intraepithelial neoplasia type 3 (PanIN-3)
	Intraductal papillary mucinous neoplasm with low or intermediate grade dysplasia
	Intraductal papillary mucinous neoplasms
	High-grade dysplasia
	Tubulopapillary intraductal neoplasia
	Mucinous cystic neoplasia with low or intermediate grade dysplasia
	Mucinous cystic neoplasia with high-grade dysplasia
Malignant	Ductal adenocarcinoma
	Adenosquamous carcinoma
	Colloids carcinoma (non-cystic mucinous carcinoma)
	Hepatoid carcinoma
	Medullary carcinoma
	Ring cell carcinoma
	Undifferentiated carcinoma
	Undifferentiated carcinoma with giant osteoclast-like cells
	Acinar cell carcinoma
	Acinar cystadenocarcinoma
	Intraductal papillary mucinous neoplasm associated with invasive carcinoma
	Mixed acinar-ductal carcinoma
	Mixed acinar-neuroendocrine carcinoma
	Mixed acinar-ductal-neuroendocrine carcinoma
	Mixed ductal-neuroendocrine carcinoma
	Mucinous cystic neoplasm associated with invasive carcinoma
	Pancreatoblastoma
	Serous cystadenocarcinoma
	Solid pseudopapillary neoplasia
Neuroendocrine neoplasms	Pancreatic neuroendocrine microadenoma
	Neuroendocrine tumor (NET)
	Pancreatic, non-functioning G1, G2 NET

Category	Specific neoplasm
	G1 NET
	G2 NET
	Neuroendocrine carcinoma (NEC)
	Large cell NEC
	Small cell NEC
	Serotonin-producing NET (carcinoid)
	Gastrinoma
	Glucagonoma
	Insulinoma
	Somatostatinoma
	VIPoma
	Mature teratoma
Mesenchymal tumors	
Lymphomas	
Metastases	

The main malignant tumors of the pancreas, classified according to the WHO, include the following clinically significant groups: **pancreatic ductal adenocarcinoma (PDAC):** the most common form, accounting for the majority of malignant pancreatic tumors; **pancreatic neuroendocrine neoplasms (PanNETs):** a heterogeneous group of tumors originating from the endocrine cells of the pancreas, which differ significantly from PDAC in their biology, clinical course, and therapeutic approaches; **cystic neoplasms with malignant potential:** these include **intraductal papillary mucinous neoplasms (IPMN)** and **mucinous cystic neoplasms (MCN)**, which are considered precursor lesions with varying risks of malignant transformation; **Acinar cell carcinoma (ACC):** a rare exocrine malignancy that accounts for 1-2% of all pancreatic neoplasms in adults [2]. The anatomical distribution of tumors in the pancreas has a significant impact on the clinical picture and time to diagnosis. The distribution is as follows: head of the pancreas: 60-70% of tumors; body and tail of the pancreas: 20-25% of tumors; diffuse involvement: 10-20% of cases [3].

Pancreatic ductal adenocarcinoma (PDAC) is the most common histological subtype. Acinar cell carcinoma (ACC) is rare, accounting for 1-2% of exocrine neoplasms in adults and 15% of neoplasms in the pediatric population [2]. Due to the lack of specific early manifestations and the biological aggressiveness of the disease, diagnosis is delayed in more than 80% of cases [3]. This leads to the disease being detected at an advanced, often unresectable or metastatic stage.

A characteristic demographic profile is observed for acinar cell carcinoma (ACC). The disease has a bimodal age distribution with peaks in childhood (8-15 years) and in adulthood (peak at 60 years). There is also a significant predominance in men, with a male-to-female ratio of 3.6:1 [2]. The epidemiological profile of pancreatic cancer is closely related to the main causes and risk factors which drive these trends.

Identifying the etiological drivers and quantifiable risk factors for pancreatic cancer is not simply an academic exercise; it is the foundation upon which we build strategies for monitoring high-risk cohorts and counseling patients about modifiable risks, which represents our most tangible opportunity for early intervention. Approximately 5-10% of PDAC patients have germline mutations in known predisposition genes [4]. The presence of these mutations significantly increases the risk of developing pancreatic cancer: *BRCA1/2* (Hereditary Breast and Ovarian Cancer Syndrome); *PALB2; ATM; STK11/LKB1* (Peutz-Jeghers Syndrome); *CDKN2A* (Familial atypical multiple melanoma); mismatch repair genes (*MLH1, MSH2, MSH6, PMS2*) (Lynch syndrome); *PRSS1/SPINK1/CFTR* (Hereditary pancreatitis) [5]. The National Comprehensive Cancer Network (NCCN) recommends considering screening with magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) for mutation carriers depending on the specific gene and family history. For carriers of *STK11/LKB1* mutations, screening should begin at age 30-35. For carriers of *CDKN2A* mutations, screening is considered from age 40. For carriers of *ATM, BRCA1/2*, and *PALB2* mutations, screening should be considered starting at age 50 or 10 years before the earliest diagnosis of pancreatic cancer in the family. The American Society for Gastrointestinal Endoscopy (ASGE) recommends annual screening with MRI/MRCP or EUS for all *BRCA1/2* mutation carriers, regardless of family history, with screening starting at age 50 or 10 years before the earliest diagnosis of pancreatic cancer in the family [6].

Chronic pancreatitis has been found to be a significant independent risk factor for the development of pancreatic cancer [5]. The relationship between DM and PDAC is complex and is described as a „double causal relationship“. Long-standing type 2 diabetes is an established risk factor for PDAC. On the other hand, newly diagnosed diabetes, especially when associated with weight loss in a patient without metabolic syndrome, should raise high clinical suspicion for underlying PDAC. Data show that approximately one in 125 patients with newly diagnosed diabetes has PDAC, representing an eightfold increase in risk compared to the general population [3, 7]. A number of lifestyle factors contribute to the risk of pancreatic cancer. **Smoking** is the factor with the strongest pos-

itive association, doubling the risk of developing pancreatic cancer. Obesity is a strong variable risk factor associated with increased morbidity and potentially poorer treatment outcomes. Excessive alcohol consumption is a risk factor. The risk is particularly high in individuals with the ALDH22* allele, common in East Asian populations, due to the accumulation of acetaldehyde. Diets rich in red and processed meat may increase the risk, in part through the formation of advanced glycation end products (AGEs) [5].

Understanding the molecular pathogenesis of pancreatic cancer is crucial for the development of targeted therapies and the identification of prognostic biomarkers. Advances in genomics have revealed a complex network of genetic and epigenetic changes that drive tumorigenesis, offering new opportunities for personalized medicine. The development of PDAC is a multistep process that begins with precursor lesions. The best-characterized precursor lesions include: pancreatic intraepithelial neoplasia (PanIN): these are microscopic lesions in the smaller pancreatic ducts that progress from low grade (PanIN-1) to high grade (PanIN-3), which represents carcinoma *in situ* [5]; cystic neoplasms: intraductal papillary mucinous neoplasms (IPMN), which are also considered precursor lesions, are characterized by point mutations in the KRAS gene and can progress to invasive carcinoma [4]. The different histological subtypes of pancreatic cancer are characterized by specific genetic alterations (Table 2).

Table 2. Molecular mechanisms of pancreatic cancer

Tumor type	Key altered genes/ pathways	Prevalence/Significance
PDAC	*KRAS*, *TP53*, *SMAD4*, *CDKN2A*	Activating mutations in *KRAS* are found in 90% of cases and are an early stage of tumorigenesis
PanNET	*MEN1*, *DAXX/ATRX*, mTOR pathway	Mutations in *DAXX/ATRX* are observed in 40-60% of cases and are associated with more aggressive behavior and a poorer prognosis
ACC	WNT signaling pathway (inactive mutations in *APC* or active in *CTNNB1*), DNA repair genes (*ATM, BRCA1, BRCA2, PALB2, MSH2*)	Mutations in the WNT pathway occur in ~20% of cases. Mutations in DNA repair genes create therapeutic opportunities

Identifying molecular biomarkers is essential for stratifying patients and guiding therapy. CA 19.9 is the only biomarker used in clinical practice for PDAC. Due to its low sensitivity and specificity, it is not suitable for diagnosis, but it is useful for assessing prognosis and monitoring response to treatment [4]. Germline mutations in *BRCA1/2* and *PALB2* – patients with these mutations may benefit from treatment with PARP inhibitors (e.g., olaparib) and platinum-based chemotherapy [9]. Up to 1.3% of pancreatic cancer cases are part of the Lynch syndrome spectrum and are characterized by microsatellite instability (MSI). High microsatellite instability (MSI-H) predicts response to PD-1 inhibitors, such as pembrolizumab. Circulating tumor DNA (ctDNA) has the potential for non-invasive detection of KRAS mutations (in combination with CA 19.9) to aid diagnosis, monitor response to treatment, and predict prognosis [4].

Accurate pathological assessment and staging are cornerstones of pancreatic cancer management, as they dictate the therapeutic strategy – from surgical resection to systemic therapy – and provide important prognostic information. PDAC usually presents as a solid, poorly defined mass. In contrast, ACC is often a well-defined, voluminous mass [2]. Key histological features that influence prognosis include the degree of tumor differentiation, the presence of perineural and lymphovascular invasion, and the status of resection margins. The status of the resection margins is a critical prognostic factor.

Classifications include: R0 direct: no tumor cells at the resection margin and R0 wide: tumor-negative margin >1 mm. Recent meta-analyses have clearly shown that achieving a tumor-negative margin greater than 1 mm (R0 >1 mm) is an independent prognostic factor associated with improved overall survival (OS) and disease-free survival (DFS). This applies to both patients undergoing primary resection and those treated with neoadjuvant therapy [10].

Pancreatic cancer is staged according to the TNM classification of the American Joint Committee on Cancer (AJCC). Due to significant biological differences, exocrine and neuroendocrine tumors are staged separately (Tables 3 and 4).

In terms of surgical management and extent, patients are classified into four categories which determine the therapeutic approach: resectable, borderline resectable, locally advanced unresectable, and metastatic. The presence of distant metastases defines the disease as unresectable (Table 5).

The clinical picture of pancreatic cancer is extremely diverse and often insidious, with symptoms largely determined by the anatomical location of the tumor and its biological function. The lack of early specific symptoms is a major reason for the late diagnosis of the disease. Clinical manifestations vary significantly depending on whether the tumor is located in the head, body, and/or tail of the pancreas. Tumors in the

Table 3. Staging according to AJCC 8th edition for exocrine pancreatic tumors (PDAC, ACC)

Stage	TNM	Description
0	Tis, N0, M0	Carcinoma *in situ*; no metastasis to regional lymph nodes; no distant metastasis.
IA	T1, N0, M0	Tumor ≤ 2 cm; no metastasis in regional lymph nodes; no distant metastasis.
IB	T2, N0, M0	Tumor > 2 cm and ≤ 4 cm; no metastasis in regional lymph nodes; no distant metastasis.
IIA	T3, N0, M0	Tumor > 4 cm; no metastasis in regional lymph nodes; no distant metastasis.
IIB	T1/T2/T3, N1, M0	Tumor of any size, confined to the pancreas; metastases in 1 to 3 regional lymph nodes; no distant metastases.
III	T1/T2/T3, N2, M0 or T4, Any N, M0	Tumor of any size with metastasis in ≥4 regional lymph nodes; OR tumor involving major blood vessels (celiac trunk, superior mesenteric artery, common hepatic artery), regardless of lymph node status; no distant metastasis.
IV	Any T, Any N, M1	Presence of distant metastases.

Table 4. AJCC staging for well-differentiated pancreatic neuroendocrine tumors (pNETs)

AJCC Stage	Grouping by stage	Stage description
I	T1, N0, M0	Tumor < 2 cm, confined to the pancreas. No lymph node involvement or distant metastases.
II	T2, N0, M0 or T3, N0, M0	Tumor ≥ 2 cm but ≤ 4 cm, confined to the pancreas; OR tumor > 4 cm or infiltrating the duodenum or common bile duct. No lymph node involvement or distant metastases.
III	T4, N0, M0 or Any T, N1, M0	Tumor infiltrating adjacent organs or major blood vessels; OR tumor of any size with regional lymph node involvement. No distant metastases.
IV	Any T, Any N, M1	Tumor of any size, with or without lymph node involvement, but with distant metastases.

Table 5. Criteria for resectability

Category	Arterial involvement	Venous involvement
Resectable	No tumor contact with the celiac trunk (CT), superior mesenteric artery (SMA), or common hepatic artery (CHA).	No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV), or contact ≤180° without irregularities along the venous contour.
Borderline resectable	Solid tumor contact with SMA ≤180°. Solid tumor contact with CHA without involvement of CT or hepatic artery bifurcation, allowing resection and reconstruction.	Solid tumor contact with SMV or PV >180°, or contact ≤180° with irregularities along the contour, or venous thrombosis, but with adequate proximal and distal margins allowing safe resection and reconstruction.
Unresectable	Solid tumor contact with SMA or CT >180°. Involvement of the first jejunal branch of the SMA.	Tumor infiltration or thrombosis of the SMV or PV that does not allow reconstruction. Contact with the most proximal jejunal vein that drains into the SMV.

head of the pancreas often cause symptoms of biliary obstruction due to compression of the distal common bile duct. Typical manifestations include painless progressive jaundice, dark urine, and itching. Physical examination may reveal a palpable, non-enlarged gallbladder, known as Courvoisier's sign. Tumors in the body and tail of the pancreas are diagnosed at a more advanced stage due to their nonspecific symptoms. Patients often complain of dull, constant pain in the abdomen or back, unexplained weight loss, weakness, and anorexia [3].

Some types of pancreatic tumors can cause specific syndromes associated with hormonal overproduction or enzyme release. Functioning PanNETs tumors produce hormones that lead to characteristic clinical syndromes, such as hypoglycemia (in insulinoma) or severe peptic ulcers and diarrhea (in gastrinoma) [11]. Schmid's Triad – some acinar cell carcinomas (ACC) are associated with this paraneoplastic syndrome, also known as lipase hypersecretion syndrome. It includes the triad of subcutaneous fat necrosis, polyarthralgia (due to fat necrosis in the bones), and peripheral eosinophilia [2]. Trousseau's syndrome – PDAC is associated with a hypercoagulable state, which can manifest as migratory superficial thrombophlebitis. Signs of advanced disease reflect local tumor spread and the presence of distant metastases. They include: a palpable mass in the epigastrium; hepatomegaly due to liver metastases; ascites caused by peritoneal carcinomatosis; palpable supraclavicular (Virchow's node) or peri-umbilical (Sister Mary Joseph's node) lymph nodes [3].

The diagnostic and staging process for suspected pancreatic cancer is a critical, time-sensitive pathway aimed at confirming the diagnosis, determining the extent of the disease, and establishing resectability. All these elements are essential for developing an effective treatment plan. Imaging studies are at the heart of the diagnostic process. Abdominal ultrasound (US) is the first test performed for abdominal pain or jaundice. It can detect dilation of the bile ducts, but has low sensitivity (50-70%) for direct detection of tumors. Multidetector computed tomography (CT) is the gold standard for diagnosis and staging. A two-phase CT scan with a pancreatic protocol (arterial and portal venous phase) is mandatory to assess the primary mass, blood vessel involvement, and the presence of distant metastases. Magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP) has sensitivity and specificity comparable to those of CT. It is often used in difficult-to-diagnose cases, for better imaging of the biliary anatomy, and in cystic neoplasms [3]. Imaging studies of somatostatin receptors – methods such as PET/CT with gallium-68 are specifically designed for staging pancreatic neuroendocrine neoplasms (PanNETs) which express somatostatin receptors.

Histological confirmation is key to treatment planning. A pathological diagnosis is mandatory for patients with unresectable, borderline resectable, or metastatic disease before starting chemotherapy or radiotherapy. However, it is not necessary before surgery for clearly resectable lesions. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is the safest and most sensitive procedure for obtaining tissue from the primary tumor. Percutaneous biopsy under US or CT guidance is the procedure of choice in patients with metastatic liver disease [3].

Carbohydrate antigen 19-9 (CA 19.9) is the only biomarker used in clinical practice for PDAC. It is not suitable for diagnosis due to false negative and false positive results. Its main role is in assessing prognosis and monitoring response to treatment [4]. Alphafetoprotein (AFP) may be elevated in young patients with acinar cell carcinoma (ACC), and serum lipase may serve as a marker in patients with ACC with lipase hypersecretion syndrome [2].

The overall workflow integrates imaging and pathology data to assess resectability. In some cases, additional procedures are required. A staging laparoscopy procedure is considered in patients at high risk for metastatic disease (e.g., large tumors in the body/tail, high tumor markers) to detect small peritoneal or hepatic metastases that are not visible on CT.

Surgical resection remains the only potential treatment for localized pancreatic cancer. The choice of procedure is dictated by the location and biology of the tumor, and the results are highly dependent on the experience of the surgical center, the technique, and the integration of the operation into a multimodal treatment plan. **The main surgical procedures** are determined by the anatomical location of the tumor. Pancreatoduodenectomy (Whipple procedure) is the procedure of choice for tumors located in the head of the pancreas [3]. Distal pancreatectomy is used for tumors of the body or tail of the pancreas, often in combination with splenectomy [12]. **Total pancreatectomy** is reserved for selected cases with extensive disease involving the entire gland [12].

For selected PanNETs and benign or low-grade cystic lesions, parenchyma-preserving procedures are preferred in order to preserve endocrine and exocrine function. **Enucleation** involves removal of the tumor only, while **central pancreatectomy** is resection of the middle part of the pancreas [12]. In borderline resectable disease, resection and reconstruction of the portal vein (PV) or superior mesenteric vein (SMV) is an accepted procedure and is not associated with a worse prognosis. **Arterial resection and reconstruction is** an approach which is still considered experimental and is performed only in specialized centers [3].

A growing body of level 1 evidence based on meta-analyses of randomized clinical trials compares minimally invasive pancreatic surgery (MIPS) with open surgery (Table 6).

Table 6. Comparison of MIPS results versus open surgery (data from meta-analysis)

Indicator	MIPS vs. open surgery
Intraoperative blood loss	Reduced by an average of 137 ml
Length of hospital stay	Reduced by an average of 1.3 days (significant only in distal pancreatectomy: -2 days)
Surgical site infections (in PD)	Reduced (OR 0.4)
Duration of surgery (in PD)	Increased by an average of 75 minutes

The incidence of overall morbidity and mortality are comparable between the two approaches, suggesting that MIPS is a safe and feasible alternative in experienced hands [13]. The most common clinically significant early complications include postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE), and post-pancreatectomy hemorrhage (PPH). Key long-term functional consequences include exocrine insufficiency requiring enzyme re-

placement therapy, and endocrine insufficiency (diabetes mellitus).

Surgery is often only one component of a broader treatment strategy that includes systemic therapies to address micrometastatic disease. The critical role of systemic therapy in the management of pancreatic cancer is undeniable. Due to the high risk of micrometastatic disease at the time of diagnosis, a multimodal approach integrating chemotherapy, and sometimes radiotherapy, with surgery is now the standard of care for most patients. The goals of perioperative therapy are to increase the chances of R0 resection and to treat early micrometastatic disease. It is the standard approach for borderline resectable disease. The chemotherapy regimens used are FOLFIRINOX and gemcitabine plus nab-paclitaxel [3]. Adjuvant treatment is recommended for patients after R0/R1 resection with good general condition. Standard regimens include modified FOLFIRINOX and gemcitabine plus capecitabine, administered for a total of six months. Although both regimens are standard options, modified FOLFIRINOX is now the preferred regimen for medically fit patients after resection, based on the better survival results demonstrated in the PRODIGE 24/CCTG PA6 study [15], compared to the gemcitabine-based regimen validated in ESPAC-4 [16].

The choice of first-line chemotherapy for metastatic PDAC depends on the patient‘s performance status (PS) and age (Table 7).

Table 7. First-line chemotherapy for metastatic PDAC

Regimen	Indicated patient population	Key study result (median OS)
FOLFIRINOX	Good performance status (PS 0-1), age <75	11.1 months [17]
Gemcitabine + nab-paclitaxel	Good performance status (PS 0-2)	8.5 months [18]

After disease progression, second-line therapy is considered. Options include oxaliplatin-based regimens with fluorouracil (e.g., OFF) or nanoliposomal irinotecan (nal-IRI) with fluorouracil [19].

Targeted, biological, and supportive therapies aim to maintain disease control with lower toxicity after induction chemotherapy. Targeted approaches exist for molecularly defined subgroups: **olaparib**: as maintenance therapy for patients with germline *BRCA1/2* mutations who have not progressed on first-line platinum chemotherapy. **Pembrolizumab**: for tumors with mismatch repair deficiency (dMMR) or high microsatellite instability (MSI-H). **Larotrectinib**: for tumors carrying an NTRK gene fusion [19].

Therapeutic options for advanced or metastatic well-differentiated PanNETs are diverse and include: **Somatostatin analogues (SSAs):** Octreotide LAR and Lanreotide Autogel for antiproliferative effect and symptom control. **Peptide receptor radionuclide therapy (PRRT):** use of agents such as 177Lu-Dotatate for SSTR-positive tumors. **Targeted agents:** Everolimus (mTOR inhibitor) and Sunitinib (tyrosine kinase inhibitor). **Chemotherapy:** Capecitabine and Temozolomide (CAPTEM) is a widely used regimen. Platinum-based chemotherapy (cisplatin/carboplatin + etoposide) is used for high-grade (G3) poorly differentiated neuroendocrine carcinomas (NECs) [18]. **Liver-directed therapies are** an option for managing liver metastases, including transarterial chemoembolization (TACE) and ablation [12].

Once curative or life-prolonging treatment options have been exhausted or are not the primary goal, the focus shifts to palliative care. The goal of palliative care is to provide symptom relief, improve quality of life, and address the complex physical and psychosocial needs of patients with advanced pancreatic cancer. This care is provided regardless of whether the patient is receiving active anticancer treatment. Endoscopic placement of a metal stent via ERCP is the preferred method for relieving jaundice and cholangitis. This improves liver function and allows chemotherapy to be administered. Endoscopic placement of an expandable metal stent is the most common approach to restoring oral intake. Surgical gastrojejunostomy is reserved for selected patients with longer expected survival [13].

Pain is a common and severe symptom that affects 50-60% of patients. Its management requires a multimodal approach: pharmacological: analgesics based on the WHO ladder, including Nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids. Interventional: Celiac plexus block is an effective procedure for controlling visceral pain [20]. Palliative radiotherapy can reduce tumor size and relieve localized pain [21]. Malnutrition is very common due to pancreatic exocrine insufficiency (PEI) and cancer-related cachexia. Pancreatic enzyme replacement therapy (PERT) is critical, as PEI is present in 80-90% of patients. Adequate replacement therapy improves digestion, reduces steatorrhea, and helps maintain body weight [22]. Other supportive measures include dietary counseling, nutritional supplements, and appetite stimulants. Psychosocial support for the patient and family is also important in coping with the burden of the disease [21].

The prognosis for pancreatic cancer is determined by a complex combination of tumor-specific, patient-specific, and treatment-related factors. Follow-up

after treatment is essential for the timely detection of recurrence, management of long-term treatment effects, and provision of ongoing support. The most significant factors affecting prognosis are: stage at diagnosis: this is the most critical factor; resection margin status: R0 resection with >1 mm free margin is strongly associated with better survival; lymph node status: lymph node involvement (N1/N2) is a poor prognostic indicator; histological subtype and degree of differentiation: the poor prognosis of PDAC contrasts with the better prognosis of resected ACC and well-differentiated PanNETs. In PanNETs, grade (based on Ki-67 index and mitotic count) is a key factor [23]; molecular characteristics: some mutations (e.g., *BRCA*) have prognostic consequences and therapeutic implications; Performance Status: the patient‘s overall physical condition is a major determinant of treatment tolerance and outcome.

The prognosis varies significantly depending on the histology: Acinar cell carcinoma (ACC): the median overall survival for localized disease is approximately 47 months, and for metastatic disease, 14 months [2]. Pancreatic ductal adenocarcinoma (PDAC): the overall 5-year survival rate is only 7.2%, which highlights its aggressive nature [1]. Follow-up of patients after resection is standardized and aims at early detection of recurrence. Clinical examination and CA 19.9: performed every three months; Imaging studies: CT scans of the chest, abdomen, and pelvis are recommended every six months for the first 2-3 years, and then annually [3].

DISCUSSION

Pancreatic cancer remains one of the most lethal malignancies, characterized by challenging epidemiology, late diagnosis, and complex molecular biology. Despite these difficulties, modern multimodal therapeutic paradigms integrating surgery, systemic chemotherapy, and increasingly targeted and immunotherapies offer hope for improved outcomes. For modern clinical practice, it is essential that these patients be managed by multidisciplinary teams in high-volume centers where expertise in all aspects of care can be provided. Future research should focus on developing reliable strategies for early screening of high-risk individuals and identifying new molecular targets to improve therapeutic efficacy and change the trajectory of this devastating disease.

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Ethical statements: *The authors declare that no clinical trials were used in the present study.*

The authors declare that no experiments on humans or human tissues were performed for the present study.

The authors declare that no informed consent was obtained from humans, the donors or donors' representatives participating in the study.

The authors declare that no experiments on animals were performed for the present study.

The authors declare that no commercially available immortalised human and animal cell lines were used in the present study.

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REFERENCES

1. Hidalgo M, Álvarez R, Gallego J, et al. Consensus guidelines for diagnosis, treatment and follow-up of patients with pancreatic cancer in Spain. Clin Transl Oncol. 2017;19(6):667–681.
2. Calimano-Ramirez LF, Daoud T, Jaleel A, et al. Pancreatic acinar cell carcinoma: A comprehensive review. World J Gastroenterol. 2022;28(40):5827–5844.
3. Hu JX, Zhao CF, Chen WB, et al. Pancreatic cancer: A review of epidemiology, trend, and risk factors. World J Gastroenterol. 2021;27(27):4298–4321.
4. Amaral MJ, Oliveira RC, Donato P, Tralhão JG. Pancreatic Cancer Biomarkers: Oncogenic Mutations, Tissue and Liquid Biopsies, and Radiomics – A Review. Dig Dis Sci. 2023;68(7):2811–2823.
5. Tacelli M, Partelli S, Arcidiacono PG. Pancreatic Neuroendocrine Neoplasms: Classification and Novel Role of Endoscopic Ultrasound in Diagnosis and Treatment Personalization. United European Gastroenterol J. 2024;13(1):34–43.
6. Facing Our Risk of Cancer Empowered. Pancreatic Cancer Screening. FORCE; 2025.
7. Pannala R, Basu A, Petersen GM, Chari ST. New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. Lancet Oncol. 2009;10(1):88-95.
8. American Cancer Society. Pancreatic Neuroendocrine Tumor (pNET) Stages. ACS; 2025.
9. Lellouche L, Palmieri LJ, Dermine S, et al. Systemic therapy in metastatic pancreatic adenocarcinoma: current practice and perspectives. Ther Adv Med Oncol. 2021;13:17588359211018539.
10. Leonhardt CS, Pils D, Qadan M, et al. Prognostic impact of resection margin status on survival after neoadjuvant treatment for pancreatic cancer: systematic review and meta-analysis. Ann Surg Open. 2024;5(1):e272.

11. American Cancer Society. Surgery for Pancreatic Neuroendocrine Tumor (pNET). ACS; 2024.
12. Wang M, Lozano MD, Cai G. The World Health Organization System for Reporting Pancreaticobiliary Cytopathology: Standardized Categories and Practical Approaches to Pancreatic Lesions. J Clin Transl Pathol. 2024;4(3):122-135.
13. Pfister M, Probst P, Müller PC, et al. Minimally invasive versus open pancreatic surgery: meta-analysis of randomized clinical trials. BJS Open. 2023;7(2):zrad007.
14. Tinguely P, Salinas CH, Raptis DA, et al. Analysis of Short-Term Outcomes in Pancreatic Surgery with Vascular Resection from a Prospective Multicenter Global Study. Ann Surg Oncol. 2025;32(12):8870-8880.
15. Conroy T, Hammel P, Hebbar M, et al. Modified FOLFIRINOX for Resected Pancreatic Cancer. N Engl J Med. 2018;379(25):2395-2406.
16. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet. 2017;389(10073):1011-1024.
17. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817-25.
18. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691-703.
19. Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. N Engl J Med. 2019;381(4):317-327.
20. Penev G, Grigorov E, Georgiev S. Contemporary principles and classification of peripheral nerve blocks. Meditsinski Pregled. 2022;58(1):11-20.
21. Baylor College of Medicine. Palliative Care for Pancreatic Cancer.[Internet]. BCM; 2024. Available from: https://www.bcm.edu/healthcare/specialties/oncology/cancer-types/gastrointestinal-cancers/pancreatic-cancer/palliative-care
22. Viatris UK. Pancreatic cancer and PEI. [Internet]. Creon.co.uk; 2024. Available from: https://www.creon.co.uk/en-gb/hcp/efficacy-and-tolerability/pancreatic-cancer
23. American Cancer Society. Survival Rates for Pancreatic Neuroendocrine Tumors (pNETs). [Internet[. ACS; 2025. Available from: https://www.cancer.org/cancer/types/pancreatic-neuroendocrine-tumor/detection-diagnosis-staging/survival-rates.html