International Journal of Medical and Health Research
www.medicalsciencejournal.com
ISSN: 2454-9142
Received: 18-01-2025, Accepted: 19-02-2025, Published: 06-03-2025
Volume 11, Issue 2, 2025, Page No. 16-25

Histopathology of pancreatic cancer: A comprehensive review

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Abstract
Pancreatic cancer is one of the most difficult malignancies to diagnose because it early stages are often asymptomatic and the overlapping features with other forms of pancreatic disorders. In regions where healthcare resources are constrained, the true burden is underestimated, as many cases either go undiagnosed or are misclassified as other diseases with similar symptoms. Histopathology investigation plays a crucial role in establishing a definitive diagnosis. Common features such as poorly differentiated glandular structures, significant desmoplasia, and the unique tumor micro-environment defined by hypovascularity highlight the aggressive nature of pancreatic adenocarcinoma. Cytological techniques, particularly endoscopic ultrasound-guided fine-needle aspiration have revolutionized the diagnostic landscape, enabling a broader scope of pancreatic neoplasms. The integration of morphological assessments with background features such as necrosis and mucin content enhances diagnostic accuracy and improved patient outcomes.

Keywords: Pancreatic cancer, Neoplasia, biomarkers

Introduction

Globally, pancreatic cancer is one of the deadliest forms of cancer, with alarmingly low survival rates. In 2015, pancreatic cancer caused about 411,600 deaths worldwide [1]. In terms of cancer-related mortality, pancreatic cancer ranks as the fifth most common cause of death in the United Kingdom [2] and the third most common in the United States [3]. The majority of new cases (about 70%) occur in developed countries, with the incidence in 2012 reflecting this pattern [4].

The incidence of pancreatic cancer is strongly age-related, rarely occurring before the age of 40, with more than half of pancreatic adenocarcinoma cases diagnosed in individuals over 70 years old [5]. Several risk factors are associated with the development of pancreatic cancer, including smoking, obesity, diabetes, and certain rare genetic syndromes. Notably, approximately 25% of pancreatic cancer cases are linked to smoking [6], and 5–10% are attributed to inherited genetic mutations [5].

Pancreatic cancer develops when abnormal cell growth occurs in the pancreas, a gland located behind the stomach, resulting in the formation of a mass. These cancerous cells have the potential to invade surrounding tissues and metastasize to other parts of the body [7]. There are several types of pancreatic cancer, with pancreatic adenocarcinoma being the most common, accounting for approximately 90% of cases [4]. Prognosis for pancreatic adenocarcinoma is particularly poor, with only 25% of individuals surviving one year post-diagnosis and approximately 12% surviving for five years [8]. However, early-stage diagnoses improve the five-year survival rate to around 20%. In contrast, neuroendocrine tumors of the pancreas are associated with better outcomes, with 65% of patients surviving five years post-diagnosis, though survival rates vary significantly depending on the specific tumor type [4].

Methodology

The study data were collected by searching Google Scholar, Science Direct, PubMed, Scopus, Researchgate, and National Center for Biotechnology Information. The search results were limited to full articles published in English, and a total of (n=205) publications were identified using the present study's keywords and criteria were "Pancreatic cancer", "Pancreatic adenocarcinoma", "Acinar cell carcinoma", "Adenosquamous carcinomas", and "Pancreatic neuroendocrine tumors". Duplicate scientific papers were excluded. Discrepancies in the data extraction were resolved through discussion and consultation with the team of reviewers. The information of the literature search, inclusion, and exclusion criteria are summarized in Fig. 1.

Result and discusion

Normal pancreas

The pancreas is a compound tubuloacinar, lying behind the stomach and extending transversely from the spleen to the loop of duodenum. The pancreas is located behind the stomach in the upper left abdomen. It is surrounded by other organs including the small intestine, liver, and spleen. It is spongy, about six to ten inches long, and is shaped like a flat pear or a fish extended horizontally across the abdomen [9].

Pancreas is the main enzyme producing accessory gland of the digestive system. It plays an essential role in converting the food we eat into fuel for the body's cells. The pancreas has two main functions: an exocrine function that helps in digestion and an endocrine function that regulates blood sugar [10].

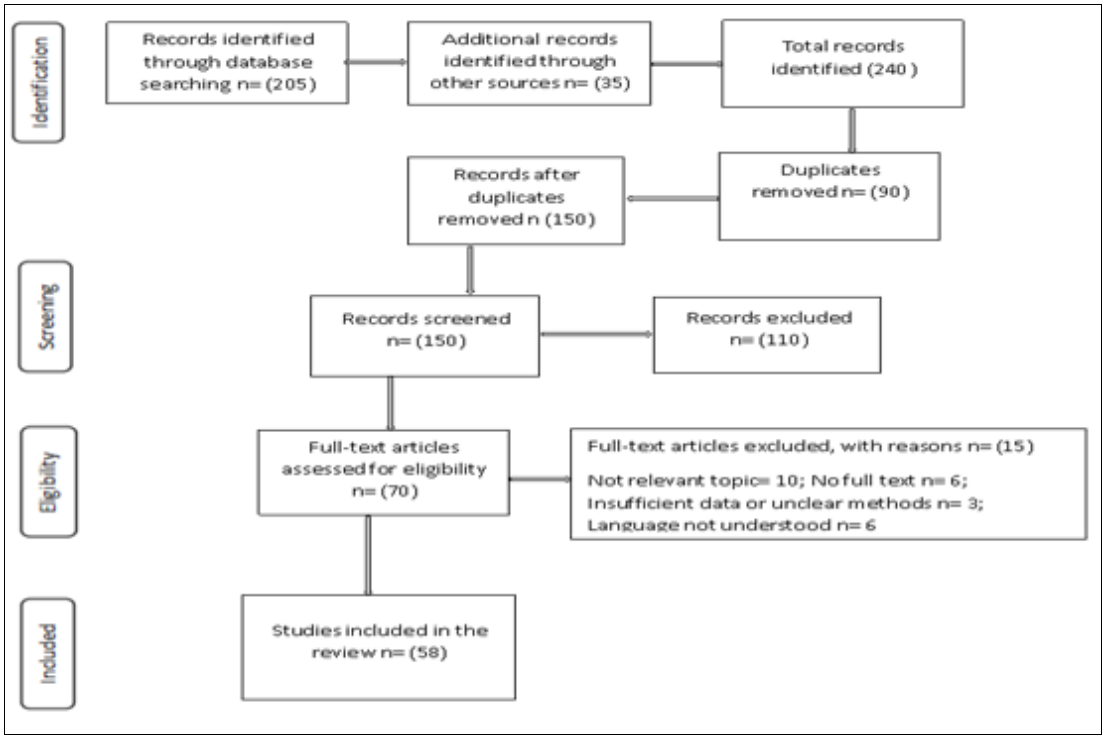

Fig 1: PRISMA flowchart of literature search, inclusion, and exclusion criteria

Epidemiology of pancreatic cancer

Pancreatic cancer is a highly lethal malignancy with a relatively low incidence globally, yet it is one of the leading causes of cancer-related deaths due to its poor prognosis. In 2020, an estimated 495,773 new cases of pancreatic cancer were reported worldwide, making it the 12th most common cancer. However, its impact on mortality is disproportionate, as it ranks 7th among cancer-related deaths globally, accounting for approximately 466,000 deaths in the same year [11]. The global incidence and mortality rates are projected to increase, with more cases expected due to factors such as aging populations, rising obesity, and smoking prevalence, particularly in developing countries [12].

The highest incidence rates of pancreatic cancer are observed in developed countries, particularly in North America and Europe, where rates are around 7-12 cases per 100,000 people per year. For example, the United States has one of the highest pancreatic cancer incidence rates, with approximately 13 per 100,000 people [13]. Europe, particularly in countries like Hungary and the Czech Republic, also sees elevated rates due to lifestyle factors such as smoking, alcohol consumption, and dietary habits. In contrast, regions like Asia and Africa report lower incidence rates, ranging from 1-5 per 100,000 people, but these rates are on the rise due to increased life expectancy and urbanization [13].

Despite lower incidence rates in some parts of the world, the prognosis for pancreatic cancer remains grim globally, with a 5-year survival rate of less than 10% in many countries [8]. Late diagnosis is a major contributing factor, as over 80% of pancreatic cancer cases are detected at an advanced or metastatic stage, limiting treatment options [3]. In Africa, pancreatic cancer is less frequently diagnosed compared to developed regions, with an incidence rate of about 2-3 cases per 100,000 individuals. The disease is under-reported in many parts of the continent due to limited access to healthcare, diagnostic tools, and cancer registries. In sub-Saharan Africa, where healthcare resources are strained, the true burden of pancreatic cancer is likely underestimated, as many cases go undiagnosed or are misclassified as other diseases with similar symptoms [11].

Risk factors contributing to the rising incidence of pancreatic cancer in Africa include increasing rates of tobacco smoking, alcohol use, diabetes, and obesity, mirroring global trends. Additionally, chronic infections like hepatitis and the growing prevalence of non-communicable diseases contribute to the rise in pancreatic cancer cases on the continent. Despite the relatively low incidence, the mortality rate in Africa remains high due to limited treatment options and late-stage diagnosis. In Nigeria, pancreatic cancer is rare, but its incidence has been gradually increasing, especially in urban centers where lifestyle changes, such as Western dietary patterns, increased smoking, and sedentary behavior, are becoming more prevalent. Data on the exact incidence of pancreatic cancer in Nigeria are limited, with estimates suggesting around 1-3 cases per 100,000 people [14]. However, due to the lack of comprehensive cancer registries and inadequate healthcare infrastructure, many cases likely go unreported, and the actual burden may be higher [14]. In Nigeria, like in much of Africa, pancreatic cancer is often diagnosed at an advanced stage, which severely limits treatment options. Access to specialized diagnostic tools like CT scans, MRI, and endoscopic ultrasound, which are essential for detecting pancreatic cancer early, is limited to a few urban hospitals. Additionally, the lack of awareness about pancreatic cancer and its risk factors, coupled with a high burden of infectious diseases and poverty, further complicates timely diagnosis and treatment. The major risk factors for pancreatic cancer in Nigeria are similar to global trends, with smoking, alcohol use, obesity, and diabetes being significant contributors. However, there is a notable gap in public health initiatives aimed at cancer prevention and early detection, and the healthcare system faces challenges in managing non-communicable diseases like cancer [14].

Pathogenesis of pancreatic cancer

The development and progression of pancreatic cancer is a multistep process. Precursor lesions for pancreatic adenocarcinoma include Intraepithelial Pancreatic Mucinous Neoplasms (IPMNs) and Pancreatic Intraepithelial Neoplasia (PanIN). The most common antecedent lesion of pancreatic cancer arises in small ducts and ductules and is called PanIN [15, 16].

Based on cellular and nuclear atypical grades, PanIN lesions are divided into low-grade (PanIN-1A/B) to high (PanIN-3) lesions [17,18]. Several changes, which occur in key genes (KRAS, CDKN2, TP53, SMAD4/DPC4, and BRCA2) are accumulated. Deregulated signaling pathways, stromal associated factors, and mRNAs serve as fuel for the development pancreatic cancer. KRAS is mutated, oncogenic miRNAs are overexpressed, and stromal associated factors are activated in PanIN-1 lesions. Mucin 1 is overexpressed, and inactivating mutations in the p16/CDKN2A gene are observed in PanIN-2 lesions. Finally, PanIN-3 lesions are associated with inactivating mutations in TP53, BRCA2, and SMAD4 [19].

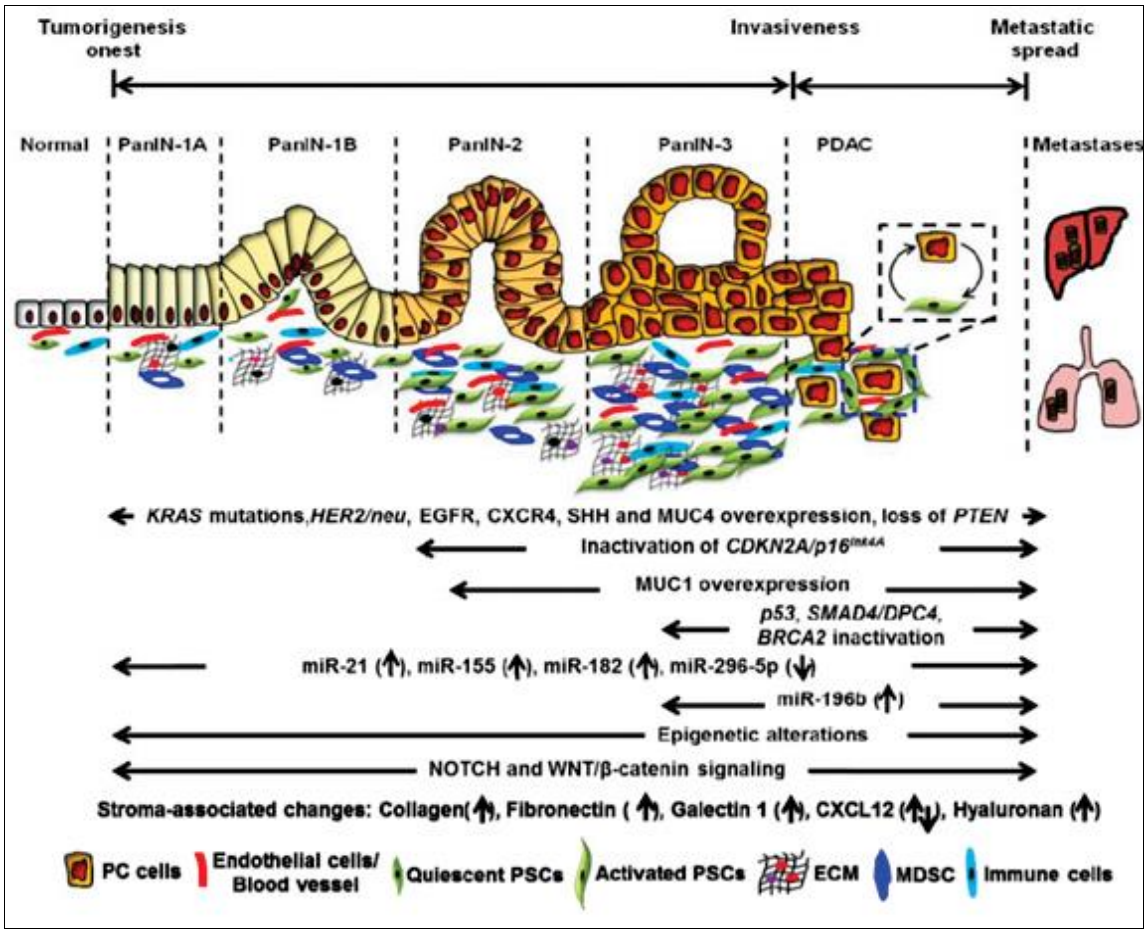

Fig 2: Histopathological and molecular changes in the pathogenesis of pancreatic cancer. Kirsten rat sarcoma oncogene homolog (KRAS), Cyclin-dependent kinase inhibitor 2 (CDKN2), Tumor protein 53 (TP53), Mother against decapentaplegic homolog 4/Deleted in pancreatic cancer 4 (SMAD4/DPC4), Breast cancer type 2 (BRCA2), Human epidermal growth factor receptor 2 (Her-2/neu), Epidermal growth factor receptor (EFGR), chemokine receptor type 4 (CXCR4), Sonic hedgehog (Shh), Mucin 4 (MUC4), Phosphatase and tensin homolog (PTEN), Motif chemokine 12 (CXCL12) [18].

Precancerous lesion

Exocrine pancreatic cancers are believed to arise from several types of precancerous lesions, though not all of these lesions progress to cancer. With the increasing use of CT scans, more lesions are being detected, but not all require treatment [6]. Aside from pancreatic serous cystadenomas, which are almost always benign, four types of precancerous lesions are recognized. The first type is pancreatic intraepithelial neoplasia (PanIN). These microscopic abnormalities are often found in autopsies of individuals with no diagnosed cancer. PanIN lesions may progress from low to high grade and eventually become tumors. More than 90% of cases, regardless of grade, carry a faulty KRAS gene. In grades 2 and 3, additional gene mutations, such as in CDKN2A (p16), p53, and SMAD4, are frequently found [5]

The second type is intraductal papillary mucinous neoplasm (IPMN), macroscopic lesions present in about 2% of all adults, with the rate increasing to 10% by age 70. IPMNs carry a 25% risk of progressing to invasive cancer. They are associated with KRAS gene mutations in 40-65% of cases, as well as mutations in GNAS (Gs alpha subunit) and RNF43, which affect the Wnt signaling pathway. Even after surgical removal, individuals with IPMNs remain at an increased risk for developing pancreatic cancer [6].

The third type is pancreatic mucinous cystic neoplasm (MCN), which mainly occurs in women. MCNs may remain benign or progress to cancer. When these lesions grow large, cause symptoms, or exhibit suspicious features, they are typically removed surgically, often with successful outcomes [20]

The fourth type is intraductal tubulopapillary neoplasm, a lesion recognized by the WHO in 2010, making up 1–3% of all pancreatic neoplasms. The mean age at diagnosis is 61 years (with a range of 35–78 years). Approximately 50% of these lesions become invasive. Accurate diagnosis relies on histology, as these lesions are difficult to distinguish from other types based on clinical or radiological features [21].

Invasive Pancreatic Cancer

The genetic mutations associated with ductal adenocarcinoma are well understood, with comprehensive exome sequencing available for common tumor types. Four key genes are frequently mutated in pancreatic adenocarcinomas:

1. KRAS mutations are present in about 95% of cases.
2. CDKN2A mutations also occur in 95% of cases.
3. TP53 mutations are found in 75% of cases.
4. SMAD4 mutations occur in 55% of cases and are particularly linked to a poor prognosis [6].

Additionally, mutations or deletions in the SWI/SNF gene complex are present in 10–15% of adenocarcinomas [5].

Research has also examined the genetic alterations in other forms of pancreatic cancer and precancerous lesions. Transcriptomics and mRNA sequencing have revealed that 75% of human genes are expressed in pancreatic tumors. Around 200 genes are more specifically expressed in pancreatic cancer when compared to other tumor types, providing further insights into its molecular characteristics [22].

Pancreatic Neuroendocrine Tumors (PanNETs)

The small minority of tumors that arise elsewhere in the pancreas are mainly pancreatic neuroendocrine tumors (PanNETs) [23]. These neuroendocrine tumors (NETs) are a diverse group of benign or malignant tumors originating from the body's neuroendocrine cells, which integrate the nervous and endocrine systems. While NETs can develop in most organs, including the pancreas, malignant PanNETs are considered rare. PanNETs are categorized into functioning and nonfunctioning types, based on their hormone production. The functioning PanNETs secrete hormones like insulin, gastrin, and glucagon into the bloodstream, often in large quantities, leading to severe symptoms such as low blood sugar. This early presentation of symptoms can aid in relatively early detection. The most common functioning PanNETs are insulinomas and gastrinomas, named after the hormones they produce. On the other hand, nonfunctioning PanNETs do not secrete hormones in significant amounts to cause noticeable symptoms. As a result, nonfunctioning PanNETs are frequently diagnosed at a more advanced stage, after the cancer has metastasized to other parts of the body [24]. The terminology and classification of PanNETs have evolved over time. Historically referred to as "islet cell cancers", it is now understood that they do not actually arise from islet cells as once believed [24].

The genetic mutations in pancreatic neuroendocrine tumors (PanNETs) differ significantly from those in exocrine pancreatic cancer [25]. One key distinction is the absence of KRAS mutations, commonly found in exocrine cancers. Instead, MEN1 gene mutations are notable, particularly in individuals with MEN1 syndrome, where primary tumors develop in multiple endocrine glands. Approximately 40–70% of individuals with a hereditary MEN1 mutation will eventually develop a PanNET [26]. In addition, other frequently mutated genes in PanNETs include DAXX, mTOR, and ATRX, which also contribute to the distinct molecular profile of these tumors [24].

Forms of pancreatic cancer

Pancreatic cancers can be broadly classified into two major categories. Approximately 95% of cases originate in the part of the pancreas responsible for producing digestive enzymes, known as the exocrine component. Although there are several subtypes of exocrine pancreatic cancer, their diagnosis and treatment share many similarities. A much smaller proportion of pancreatic cancers develop in the endocrine (hormone-producing) tissue and are known as pancreatic neuroendocrine tumors (PanNETs). These two categories exhibit distinct clinical characteristics [27]. Both exocrine pancreatic cancers and PanNETs primarily affect individuals over the age of 40 and tend to be slightly more prevalent in men. However, there are rare subtypes that are more common in women or children, adding to the diversity of clinical presentations and demographic variations across these cancer types [28].

Exocrine Cancers

The exocrine group of pancreatic cancers is predominantly comprised of pancreatic adenocarcinoma, the most common type, accounting for about 85% of all pancreatic cancers [5]. Most of these cancers arise in the ducts of the pancreas and are specifically referred to as pancreatic ductal adenocarcinoma (PDAC) [27]. Although the pancreatic ductal epithelium, from which these cancers develop, constitutes less than 10% of the pancreas by cell volume, PDAC originates from the extensive duct system that carries secretions such as enzymes and bicarbonate away from the pancreas [28]. Approximately 60-70% of these adenocarcinomas occur in the head of the pancreas [5].

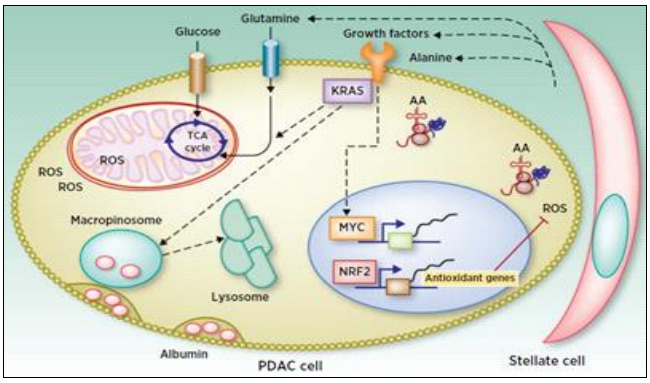

Fig 3: Pancreatic ductal adenocarcinoma metabolism. The interplay between adenocarcinoma cells and stellate cells. Tricarboxylic acid (TCA) cycle. Pancreatic adenocarcinoma (PDAC) [29]

In pancreatic ductal adenocarcinoma cells, metabolic changes occur by activation of KRAS and MYC, which promote glutaminolysis, glycolysis, and macropinocytosis (RAS-mediated phenotype that increases the consumption of proteins such as albumin, which will be digested by lysosomal enzymes to promote pancreatic cancer cell growth) [30]. Another form of exocrine pancreatic cancer is acinar cell carcinoma, which represents about 5% of exocrine cancers [30]. This type originates in the clusters of

cells (acini) that produce digestive enzymes. It can lead to the overproduction of these enzymes, causing symptoms such as skin rashes and joint pain. Cystadenocarcinomas make up about 1% of pancreatic cancers and generally have a better prognosis than other types of exocrine pancreatic cancers [30].

Pancreatoblastoma is a rare form of pancreatic cancer, mostly occurring in childhood, and has a relatively favorable prognosis. Other less common exocrine pancreatic cancers include adenosquamous carcinomas, signet ring cell carcinomas, hepatoid carcinomas, colloid carcinomas, undifferentiated carcinomas, and undifferentiated carcinomas with osteoclast-like giant cells [5]. Additionally, solid pseudopapillary tumors are rare, low-grade neoplasms that primarily affect young women and tend to have a good prognosis. Pancreatic mucinous cystic neoplasms form a broad category of pancreatic tumors with varying degrees of malignancy. These tumors are being detected more frequently due to advancements in CT scan technology, and ongoing discussions aim to determine the best ways to assess and treat them, as many are benign [31].

Signs and Symptoms of pancreatic cancer

Since pancreatic cancer usually does not cause recognizable symptoms in its early stages, it is often not diagnosed until the disease has spread beyond the pancreas [32]. This contributes to its generally poor survival rates. A notable exception to this are the functioning PanNETs, where the over-production of active hormones can lead to symptoms, depending on the hormone type [32]. Common presenting symptoms of pancreatic adenocarcinoma include:

a. Pain in the upper abdomen or back, which often spreads from around the stomach to the back. The location of the pain can provide clues about the tumor's location in the pancreas. The pain tends to worsen at night and intensifies over time, becoming severe and unrelenting [30]. In the UK, about half of all new pancreatic cancer cases are diagnosed after a visit to the emergency department due to pain or jaundice. In two-thirds of individuals, abdominal pain is the primary symptom, with jaundice accompanying it in 46% of cases, and 13% presenting jaundice without pain [33].
b. Jaundice, a yellowing of the whites of the eyes or skin, sometimes accompanied by darkened urine. This symptom results when a tumor in the head of the pancreas obstructs the common bile duct as it passes through the pancreas [38].
c. Unexplained weight loss, which may occur due to a loss of appetite or compromised exocrine function, leading to poor digestion [34].
d. Digestive issues, caused by the tumor compressing nearby organs, which can disrupt digestion and make it difficult for the stomach to empty. This can lead to nausea, a feeling of fullness, and undigested fat in stools, causing foul-smelling, fatty stools that are difficult to flush. Constipation is also common [34].
e. Diabetes, present in at least 50% of individuals with pancreatic adenocarcinoma at diagnosis [5]. While long-standing diabetes is a known risk factor for pancreatic cancer, the cancer can also induce diabetes. Newly developed diabetes in individuals over 50 could be an early sign of the disease, with these individuals having an eightfold increased risk of developing pancreatic adenocarcinoma within three years, after which the risk declines [34].
f. Symptoms of Spread: When pancreatic cancer spreads (metastasizes), it can cause additional symptoms. Typically, it first spreads to nearby lymph nodes and later to the liver, peritoneal cavity, large intestine, or lungs. Less commonly, it can spread to the bones or brain [6]. Secondary cancers in the pancreas, originating from other body parts like the kidneys, colorectal area, skin, breast, or lungs, are rare, accounting for only about 2% of pancreatic cancer cases. Surgery may be performed in such cases, either with curative intent or to alleviate symptoms [35,36].

Stages of Pancreatic Cancer

Cancer stage describes the extent of cancer in the body, such as the size of the tumor, whether it has spread, and how far it has spread from where it first formed. It is important to know the stage of the pancreatic cancer to plan the best treatment [3]. There are several staging systems for cancer that describe the extent of the cancer. Pancreatic cancer staging usually uses the TNM staging system. Based on the TNM results, a stage (I, II, III, or IV, also written as 1, 2, 3, or 4) is assigned to cancer [3].

The following stages are used for pancreatic cancer [3]:

1. **Stage 0 (carcinoma in situ):** In stage 0, abnormal cells are found in the lining of the pancreas. These abnormal cells may become cancer and spread into nearby normal tissue. Stage 0 is also called carcinoma in situ.

2. **Stage I (also called stage 1) pancreatic cancer**: In stage I, cancer has formed and is found in the pancreas only. Stage I is divided into stages IA and IB, depending on the size of the tumor.
   - Stage IA: The tumor is 2 centimeters or smaller.
   - Stage IB: The tumor is larger than 2 centimeters but not larger than 4 centimeters.

Stage I pancreatic cancer; drawing on the left shows stage lA pancreatic cancer. The cancer is in the pancreas and the tumor is 2 centimeters or smaller. An inset shows 2 centimeters is about the size of a peanut. The drawing on the right shows stage IB pancreatic cancer. The cancer is in the pancreas and the tumor is larger than 2 centimeters but not larger than 4 centimeters, an inset shows 2 centimeters is about the size of a peanut and 4 centimeters is about the size of a walnut [3].

3. **Stage II (also called stage 2) pancreatic cancer**: Stage II is divided into stages IIA and IIB, depending on the size of the tumor and where the cancer has spread.
   - Stage IIA: The tumor is larger than 4 centimeters.
   - Stage IIB: The tumor is any size, and cancer has spread to 1 to 3 nearby lymph nodes.

1. **Stage III (also called stage 3) pancreatic cancer:** In Stage III pancreatic cancer. The tumor is any size and cancer has spread to (a) 4 or more nearby lymph nodes; or (b) the major blood vessels near the pancreas. These include the portal vein, common hepatic artery, celiac axis (trunk), and superior mesenteric artery.
2. **Stage IV (also called stage 4) pancreatic cancer:** The tumor is any size and cancer has spread to other parts of the body, such as the lung, liver, or peritoneal cavity

(the body cavity that contains most of the organs in the abdomen).

Laboratory Tests of Pancreatic Cancer

1. Tumor Marker

a. Carbohydrate antigen (CA 19-9)

The most clinically useful serum tumor marker for pancreatic cancer is Carbohydrate antigen 19-9 (CA 19-9), a sialylated Lewis antigen (Lea) commonly produced in pancreatic and hepatobiliary disease but also increased in many other conditions [33]. The only marker approved by the United States Food and Drug Administration for use in the routine management of pancreatic cancer is serum cancer antigen 19-9 [37]. Unfortunately, CA19-9 lacks sensitivity or specificity for early pancreatic cancer diagnosis, despite its routine use to monitor disease progression, recurrence, and/or therapy response [38]. The low positive predictive value of CA 19-9 indicates that it cannot be used in screening, but it can contribute to making a diagnosis in symptomatic patients [39].

b. Carcinoembryonic antigen (CEA)

The plasma concentration of the tumor markers Carcinoembryonic Antigen (CEA) may be elevated in up to 50% of patients with pancreatic malignancy, but they can be elevated with other (particularly colorectal) cancers and sometimes in non-malignant
disease. Unfortunately, pancreatic cancer often presents late; by the time it is diagnosed, metastases are often present [37]. In addition, CEA levels may be elevated in colorectal, breast, gastric, lung, mesothelioma, esophageal gastric, hepatocellular, esophageal, and ovarian cancer. A non-malignant condition that may increase CEA levels are chronic liver disease, colitis, diverticulitis, irritable bowel syndrome, and jaundice [37].

c. Other tumor markers

The presence of circulating tumor cells originating from pancreatic cancer can be diagnostic, but it is present only in a few patients with metastatic disease. In contrast, circulating tumor DNA encoding mutant KRAS has been detected at the time of diagnosis in 43% of patients with localized disease, suggesting that circulating tumor DNA consisting of a panel of mutated genes such as mutated KRAS or mutated TP53 may serve as a non-invasive early diagnostic test [38]. The presence of DNA mutations in pancreatic juice has also been an area of study. Mutant P53 was found in the pancreatic juice of individuals with PanIN 2-3, intermediate and high-grade IPMN, and invasive malignancy [37]. A potential novel biomarkers for early pancreatic cancer diagnosis: First, antibody microarrays using sequential plasma samples from GEMM with pancreatic cancer. Second, the presence of the heparan sulfate proteoglycan glypican 1 on the outer layer of circulating exosomes has been observed in both GEMM and patients with earlystage disease, suggesting that exosome analysis could be useful for early diagnosis [38].

2. Cancer Stem Cells

The poor prognosis of pancreatic cancer may be caused by a prevalence of Cancer Stem Cells (CSCs). Cancer stem cells are a population of cancer cells showing stem cell-like characteristics. Cancer stem cells have the ability to self-renew and may initiate tumorigenesis. The expression of pancreatic cancer stem cell markers such as CD133, CD24, CD44, DCLK1, CXCR4, ESA, Oct4, and ABCB1 could be negative prognostic factors in pancreatic cancer and are responsible for its faster progression and its resistance to standard treatment [40].

3. Hepatobiliary Tests and Other Blood Tests

Other presentations of pancreatic cancer include obstructive jaundice, when a tumor in the head of the pancreas obstructs the common bile duct, and malabsorption. Biochemical tests of pancreatic function are rarely useful in diagnosis.18 Serum amylase and/or lipase levels are elevated in less than 50% of patients with resectable pancreatic cancers. A study by Asamer *et al*. [41] showed that plasma amylase was an independent prognostic factor in metastatic pancreatic carcinoma [37].

Histopathological features of Pancreatic Cancer

The histopathological examination of pancreatic cancer, particularly pancreatic adenocarcinoma, reveals several distinctive features that aid in its diagnosis. This type of cancer typically shows moderately to poorly differentiated glandular structures, which is a key characteristic of its aggressive nature. Diagnostic techniques include Fine-Needle Aspiration (FNA), Core Needle Biopsy, and Surgical Biopsy.

Common Microscopic Features

a. Glandular Structures: Under microscopic examination, pancreatic adenocarcinoma is often identified by the presence of abnormal glandular formations. These structures may appear disorganized and exhibit varying degrees of differentiation, with poorly differentiated tumors displaying a higher degree of cellular atypia, irregular nuclei, and increased mitotic activity [42].

b. Desmoplasia: One of the most significant histopathological features of pancreatic adenocarcinoma is desmoplasia. This refers to the formation of a dense fibrous stroma around the tumor, characterized by an abundance of extracellular matrix components such as type I collagen and hyaluronic acid. The stroma consists of various cell types, including myofibroblasts, macrophages, lymphocytes, and mast cells. This fibrotic reaction can lead to a hypovascular tumor microenvironment, resulting in inadequate blood supply and oxygen delivery to the tumor cells [5].

c. Hypovascularity and Tumor Hypoxia: The desmoplastic stroma contributes to a hypovascular environment, characterized by reduced blood vessels. This hypovascularity is a critical factor in the tumor's ability to resist therapy, as many chemotherapeutic agents rely on adequate blood flow to reach and penetrate the tumor mass. The resulting tumor hypoxia can lead to increased aggressiveness, as hypoxic conditions can activate pathways that promote metastasis and resistance to treatment [42].

d. Stromal Reactivity: The interaction between tumor cells and the stroma plays a crucial role in tumor progression. The stroma can provide support for tumor growth and survival through various growth factors and cytokines. This complex tumor-stroma interaction complicates treatment options and is a focus of ongoing research [23].

e. Necrosis and Inflammation: Areas of necrosis may be present within the tumor, often accompanied by inflammatory infiltrates. The presence of necrosis can indicate aggressive disease and is often associated with poor prognostic outcomes [33].

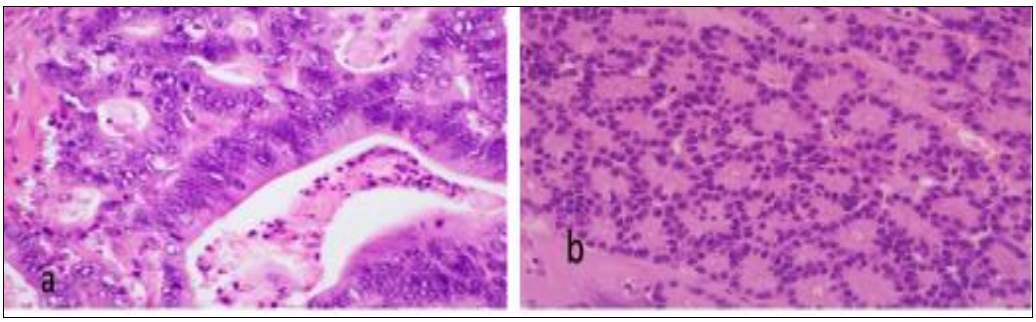

Fig 4: Illustrating (a) Pancreatic Ductal Adrenochrome [42] and (b) pancreatic acinar cell card Noma [44]

Cytological Features of Pancreatic Cancer

Cytological examination plays a crucial role in the diagnosis of pancreatic neoplasms. Traditional methods, such as pancreatic juice cytology and pancreatic duct brushing cytology, have been enhanced by the advent of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), significantly improving diagnostic accuracy for various pancreatic tumors.

Diagnostic Methods include

1. **Pancreatic Juice Cytology:** This method involves collecting pancreatic secretions, which are then examined for the presence of malignant cells. It is particularly useful for evaluating large pancreatic duct lesions, such as pancreatic ductal adenocarcinoma (PDAC) and intraductal papillary mucinous neoplasms (IPMNs). The cytological findings typically include abnormal glandular structures and atypical cells that can suggest malignancy [45].

2. **Pancreatic Duct Brushing Cytology:** Similar to pancreatic juice cytology, this technique collects cells directly from the pancreatic duct during endoscopic procedures. It is valuable for diagnosing neoplasms that obstruct the duct and allows for a detailed assessment of cellular morphology.

3. **Endoscopic Ultrasound-Guided Fine-Needle Aspiration (EUS-FNA):** EUS-FNA has revolutionized the diagnosis of pancreatic neoplasms, particularly those less directly associated with the pancreatic ducts. This method enables the collection of fine needle aspirates from lesions such as neuroendocrine neoplasms (NENs), acinar cell carcinoma (ACC), serous cystic neoplasms (SCNs), mucinous cystic neoplasms (MCNs), and solid pseudopapillary neoplasms (SPNs). The cytological material obtained can be subjected to various analyses, including immunohistochemistry and molecular testing, to confirm diagnosis [45].

The cytological diagnosis of pancreatic neoplasms primarily relies on the morphological evaluation of tumor cells, along with the examination of background features:

1. **Morphological Characteristics**: The appearance of tumor cells is critical for diagnosis. Features indicative of malignancy include:

- **Cellularity:** Increased cellularity is often observed in malignant lesions.
- **Atypical Cells:** Malignant cells typically exhibit pleomorphic nuclei, irregular contours, and hyperchromatic chromatin. In PDAC, for example, cells may form disorganized clusters with notable nuclear atypia.
- **Gland Formation:** In adenocarcinomas, abnormal glandular structures may be prominent, with the presence of poorly formed or cribriform patterns.

2. **Background Features**: The cytological background can provide additional diagnostic clues:

- **Necrosis:** Areas of necrosis within the aspirate can indicate aggressive tumor behavior. This is particularly important in differentiating between benign and malignant lesions.
- **Mucin Production:** The presence of mucin can suggest certain types of tumors, such as IPMNs or mucinous cystic neoplasms. Mucinous backgrounds are often associated with neoplastic processes and may be observed in cytological samples [45].

3. **Cytological Patterns in Specific Neoplasms**

- **Neuroendocrine Neoplasms (NENs):** Typically show small, round cells with moderate cytoplasm and finely granular chromatin. They may exhibit a trabecular or nested pattern.
- **Acinar Cell Carcinoma (ACC):** Characterized by cells resembling acinar cells with granular cytoplasm and can show high mitotic activity.
- **Mucinous Neoplasms:** Often demonstrate abundant mucin in the background, with malignant cells displaying varying degrees of atypia.

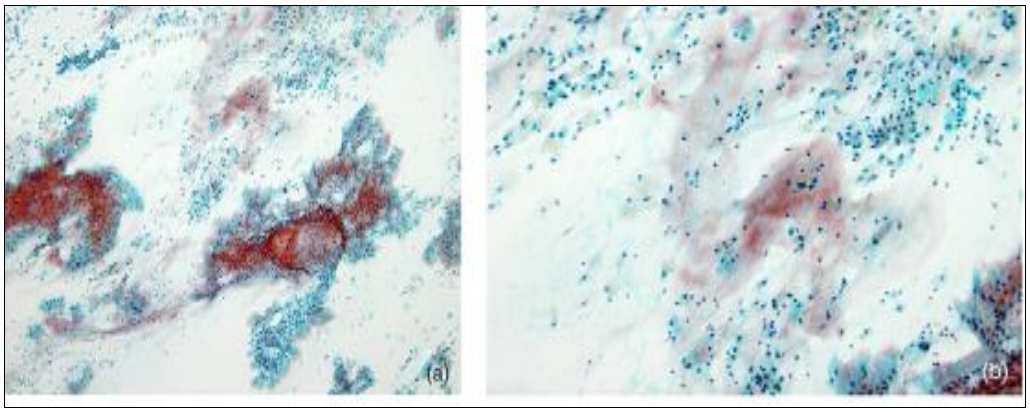

Fig 5: Mucinous background in intraductal papillary mucinous neoplasm (Papa Nicolas stain). A large amount of thick, ecosan-stained mucus appears in the background of papillary tumor cell clusters. (a) Low-power view, (b) high-power view [45]

Prevention of Pancreatic Cancer

To reduce the risk of pancreatic cancer, the American Cancer Society advises maintaining a healthy weight, avoiding smoking, and eating a diet rich in fruits, vegetables, and whole grains, while limiting the intake of red and processed meats. However, there is no consistent evidence that these measures specifically prevent pancreatic cancer [46]. A 2014 review indicated that the consumption of citrus fruits and curcumin may reduce the risk of pancreatic cancer. Additionally, whole grains, folate, selenium, and non-fried fish may offer some protective benefits, although the evidence is not definitive [47]. Further, a 2019 meta-analysis suggested that aspirin use may be associated with a reduced incidence of pancreatic cancer. However, no significant impact on pancreatic cancer mortality was found [48].

Importance of Early Diagnosis of Pancreatic Cancer

Early diagnosis of pancreatic cancer plays a pivotal role in improving patient outcomes, as this form of cancer is often asymptomatic in its initial stages and typically diagnosed at an advanced stage, when curative treatment options are limited. Pancreatic adenocarcinoma, the most common type of pancreatic cancer, has a notoriously poor prognosis, with an overall five-year survival rate of only 12% across all stages [49]. However, when diagnosed early, before the cancer has metastasized, the survival rate can increase significantly, with about 20% of patients surviving five years or more [32].

Early detection allows for the possibility of surgery, such as the Whipple procedure, which is the only treatment that offers the potential for cure. Unfortunately, less than 20% of pancreatic cancer cases are diagnosed at a stage where surgery is viable, largely due to the cancer's tendency to spread rapidly and its location deep within the abdomen, which makes early detection challenging [37]. This underscores the importance of enhancing diagnostic techniques and increasing public awareness of risk factors, such as family history, smoking, diabetes, and chronic pancreatitis, all of which are associated with higher incidences of pancreatic cancer [5].

Moreover, early diagnosis not only opens the door for curative surgery but also improves the effectiveness of other treatments like chemotherapy and radiation. Tumors that are identified at an earlier stage are typically smaller and less aggressive, making them more responsive to these therapies [7]. In addition to improving survival rates, early detection can enhance the patient's quality of life by allowing for less invasive treatments and reducing the burden of symptoms associated with advanced disease, such as severe pain, jaundice, and weight loss [33]. The challenge lies in the fact that pancreatic cancer is difficult to detect early. Symptoms are often vague and can mimic other less severe conditions, which can lead to delays in diagnosis. However, advancements in medical imaging, biomarker research, and genetic testing hold promise for earlier identification of pancreatic cancer in high-risk individuals. For example, the use of endoscopic ultrasound (EUS) and MRI, coupled with blood tests for specific tumor markers like CA 19-9, are increasingly being utilized to detect pancreatic cancer at an earlier stage [50].

Furthermore, research into the genetic mutations associated with pancreatic cancer is also aiding early detection efforts. Approximately 5-10% of pancreatic cancer cases are linked to inherited genes, and identifying individuals with these genetic predispositions could allow for earlier screening and intervention. For high-risk populations, regular surveillance may help identify precancerous lesions or early-stage tumors before they progress, thereby improving outcomes [5].

Conclusion

Pancreatic cancer remains one of the most challenging malignancies to diagnose due to its often asymptomatic nature in the early stages and the overlapping features with other pancreatic disorders. The histopathological examination plays a crucial role in establishing a definitive diagnosis. Common features such as poorly differentiated glandular structures, significant desmoplasia, and the unique tumor microenvironment characterized by hypovascularity highlight the aggressive nature of pancreatic adenocarcinoma.

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and material: Data are available from the corresponding author upon request

Competing interests: The authors declare no conflict of interest

Funding: None

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