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Pancreatic cancer; from effective prevention and early diagnosis to personalized therapy

Adrian Silaghi[1,2#], Dragos Serban[1,3#], Bogdan Gaspar[1,4], Valentin Verlas[1], Dragos Epistatu[5], Cristian Paius[2], Roxana Sfetea[6], Liliana Andronache[6], Ioana Paunica[7], Irina Ruxandra Strambu[1,8*#], Daniela Gabriela Bălan[1], Alexandru Florin Motofei[1], Vlad Denis Constantin[1,2#]

[1] *Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*

[2] *St. Pantelimon Emergency Clinical Hospital, Department of General Surgery, Bucharest, Romania*

[3] *Emergency University Hospital of Bucharest, Department of General Surgery, Bucharest, Romania*

[4] *Clinical Emergency Hospital of Bucharest, Department of General Surgery, Bucharest, Romania*

[5] *Carol Davila University of Medicine and Pharmacy, Department of Radiology, Bucharest, Romania*

[6] *Carol Davila University of Medicine and Pharmacy, Discipline of Modern Languages, Bucharest, Romania*

[7] *Carol Davila University of Medicine and Pharmacy, N.C. Paulescu National Institute, Bucharest, Romania*

[8] *Marius Nasta Pneumology Institute of Bucharest, Bucharest, Romania*

 # These authors contributed equally to this work, thus sharing the first authorship

ABSTRACT

Despite substantial improvements in survival rates for most cancers, pancreatic cancer still remains a leading cause of death from malignancy. The disease has no symptoms in the initial stages, it can early invade the surrounding organs, and treatment methods have poor long-term prognosis. In addition, this neoplasia is starting to be diagnosed more and more frequently in young people. High incidences have been found in developed regions such as Europe, North America, Australia, but recent data show that this condition is increasing in other regions as well. Pancreatic cancer involves multiple factors such as cigarette smoking, obesity, diabetes, alcohol consumption, inherited genetic factors, recent studies also correlating pancreatic cancer with abnormal metabolism of human microorganisms, blood type, as well as glucose and lipid levels. This review aims to update knowledge on the epidemiology, pathophysiology, diagnosis and treatment of pancreatic cancer. The goal is to encourage screening and early diagnosis methods, as well as to stimulate further research on this oncological topic, insufficiently studied to date.

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***Corresponding author:**

Irina Ruxandra Strambu,

Carol Davila University of Medicine and Pharmacy, Faculty of General Medicine, Marius Nasta Pneumology Institute of Bucharest, Bucharest, Romania

E-mail: istrambu@yahoo.com

Introduction

Pancreatic cancer is one of the most aggressive forms of malignancy in humans, with low survival rates, ranking as the 7th leading cause of cancer-related deaths globally [1], and it predominantly affects the elderly population. In most cases, detection occurs late, as the disease is asymptomatic in its early stages. The classic symptoms—itching, jaundice, and weight loss—indicate in 80-85% of cases the presence of an unresectable tumor due to loco-regional invasion, with 5-year survival rates below 40% [2]. This outcome is largely attributed to the pronounced cellular heterogeneity and a dense microenvironment that forms a barrier to oncological treatments, compounded by severe local immunosuppression, which hinders the ability of effector cells to recognize and eliminate neoplastic cells [1].

Thus, it is essential to identify the main risk factors for this disease within the population—such as smoking, obesity, excessive alcohol consumption, a history of pancreatitis, or a diagnosis of chronic pancreatitis or other genetic conditions—so that individuals at risk can undergo screening methods that may aid in the early diagnosis of the disease [3]. Subsequently, the clinician must decide on the patient's management strategy based on age, functional status, and individual preferences.

Surgical treatment combined with the FOLFIRINOX adjuvant therapy regimen is the only approach capable of achieving significant survival rates [4], but it comes with

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the risks associated with surgical complications and high toxicity profiles. In borderline tumors, a good response to neoadjuvant therapy can enable extensive surgery with outcomes comparable to tumors initially classified as resectable [5].

This study is a review aimed at highlighting up-to-date epidemiological data, exploring the cellular pathways through which pancreatic neoplasia develops, identifying potential interventions that could restore normal characteristics to neoplastic cells, and determining the best surgical strategy for managing this disease, which carries a grim 5-year survival prognosis.

Discussions

Epidemiology

Pancreatic cancer is an aggressive malignancy with a poor prognosis in most cases, with 5-year survival rates ranging from 0.9% to 4.25%, potentially reaching up to 17.4% in cases where successful surgical treatment is achieved [6]. Global mortality varies: 5 years after diagnosis, the survival rate in the U.S. is reported to be 10%, while in China it is 7.2%, the lowest among all types of neoplastic diseases. Survival rates show some regional variation, influenced by socioeconomic conditions, but rarely exceed 10% worldwide [7].

The prevalence of pancreatic cancer also varies across global populations. In the U.S., 60,430 new cases were detected in 2021, making it the third most common cancer by incidence that year, following lung and colorectal cancers [8]. In comparison, the European Union estimates that by 2025, 111,500 patients will die from some form of pancreatic cancer, surpassing cervical cancer in mortality rates [9]. Populations with the highest predisposition to developing pancreatic cancer at younger ages include Eastern Europe, with an incidence rate of 9.9 per 100,000 inhabitants, followed by Western Europe and North America, while East and West Asia show the lowest rates [10]. Incidence is also closely linked to the development index of a region: the more developed the region, the higher the incidence. For example, in highly developed countries like Hungary, Japan, Slovakia, and the Czech Republic, the incidence exceeds 9.1 cases per 100,000 inhabitants. In fact, the rates in developed countries are 3 to 6 times higher compared to those in developing nations [11].

The global trend regarding the incidence, prevalence, and mortality of pancreatic cancer shows an increase in these parameters within the European Union, with growth rates of up to 21.5% by 2030 compared to the incidence recorded between 2009-2018 [2]. Rising figures will also appear in Africa, Latin America, and other developing regions. Countries such as China and India will face particular challenges due to their large populations and growing economies, which will lead to the rapid development of rural and remote areas, with high potential for lifestyle changes, thus predicting significantly higher rates of incidence and mortality [12].

Risk factors for the development of pancreatic cancer include non-modifiable factors such as age, sex, blood type, the presence of diabetes, family history, and genetic factors, as well as modifiable ones, such as diet, obesity, history of acute pancreatitis, infections, and socio-economic status. All of these factors can contribute to the onset of pancreatic cancer by triggering changes at the cellular genome level, influencing the occurrence, progression, and invasion of normal cells [7].

Pancreatic cancer most often occurs in older individuals, with most patients being between 65 and 74 years old, and the average age being 70. Age is also correlated with higher mortality rates for both sexes [13]. A possible link between age and the development of pancreatic cancer could be related to the degenerative changes in telomeres that occur over time [14].

Another factor that favors the onset of pancreatic cancer is race, particularly observed in the USA, where individuals of African descent are more predisposed to developing the disease compared to Hispanics, Caucasians, and, lastly, residents of the Pacific Islands. This can be attributed to metabolic differences among various races, excessive alcohol consumption, a high fat intake, obesity, and a higher prevalence of diabetes in this population [15].

A family history of cancer can be a contributing factor in the development of pancreatic cancer. Thus, patients with a neoplastic history in their family have a 1.8 times greater risk of developing such a disease [16]. Genomic alterations through somatic mutations or within genetic syndromes such as Peutz-Jeghers syndrome, hereditary pancreatitis, familial atypical multiple mole melanoma, familial ovarian and breast cancer, Lynch syndrome, and familial adenomatous polyposis can increase the relative risk of developing pancreatic cancer [17]. Many of these syndromes lead to polygenic alterations, as seen in hereditary pancreatitis, where mutations in the PRSS1, SPINK1, and PRSS2 genes cause recurrent episodes of acute pancreatitis, with a risk of developing pancreatic cancer ranging from 7.2% to 53.5% [17]. In Lynch syndrome, mutations in MLH1, MSH2, MSH6, and PMS2 increase the risk of colon and pancreatic cancer; thus, 3.7% of patients over the age of 70 with this genetic alteration develop pancreatic neoplasia by the end of their lives [18]. Familial adenomatous polyposis with mutations in the APC gene, along with Li-Fraumeni syndrome, ataxia-telangiectasia syndrome, and CFTR mutations that cause cystic fibrosis, have a risk of developing colon cancer of less than 5% throughout their lifetime [19].

Among the modifiable factors, increased intake of red meat and excessive lipids leads to a statistically insignificant association with the development of pancreatic cancer for the general population. However, in

men, regardless of race, a consumption of over 50g of processed red meat leads to a 17% increase in baseline risk, especially when associated with more than 10g of saturated fats per day [20]. In the Western diet, in addition to high red meat intake, sugary carbonated drinks have been studied, but no correlation exists between risk and their usual consumption [21]. Moderate coffee consumption, between 1-4 cups/day, may reduce the risk of developing pancreatic cancer [22]. Other protective factors include adequate consumption of vegetables, fruits, nuts, and whole grain bread [23].

Alcohol consumption and smoking are well-known factors that contribute to the development of pancreatic cancer. The higher the alcohol consumption, the greater the risk is increased [24], along with a lower survival rate and a 9% higher risk of death caused by pancreatic neoplasm in this population group [19-21]. Smoking can be implicated in the onset and progression of pancreatic cancer, with smokers having a 37% higher risk compared to non-smokers, especially if the consumption exceeds 30 cigarettes per day [25,26]. The association of alcohol consumption and smoking amplifies the effect of each regarding the occurrence of pancreatic cancer [23,27].

Acute or chronic pancreatitis can be risk factors for development of pancreatic tumors due to injuries at this level and cellular necrosis. Sometimes, the acute form of the disease may be the first manifestation of malignancy due to obstruction of the Wirsung duct and early activation of pancreatic enzymes [28], the number of episodes correlating directly to the risk, reaching up to 9 times higher than in the normal population in individuals who have developed chronic pancreatitis due to acute cell destruction [29].

The development of a chronic form of the disease associated with a low body mass index and exocrine pancreatic insufficiency may indicate the presence of pancreatic cancer, especially if the onset occurred at an older age and the tobacco index exceeded 60 pack-years [30], with the risk of neoplasm development being 8 times higher after 5 years. Alarming figures have also been observed in those with the idiopathic form of the disease, as well as in those with cystic fibrosis [31].

Overweight and obesity are considered risk factors for many cancers, including colon, breast, and pancreatic cancer, due to their influence on multiple metabolic pathways, affecting hormonal synthesis and microbiota, thus leading to a chronic pro-inflammatory status [32]. A body mass index over 30 increases the risk of developing pancreatic cancer by up to 36%, without affecting the long-term prognosis of these patients [33]. The long-term effects of obesity have been investigated in a population of adolescents in Israel, which showed that a body mass greater than the 95th percentile compared to normal, lasting over 20 years, led to a 10.9% higher risk of developing pancreatic cancer compared to the normal-weight population [34]. Thus, sustained physical activity of over 150 minutes per week and a low-fat diet can improve the rate of development of pancreatic, colon, and breast neoplasms, especially in women with a BMI > 25 kg/m² [27].

Pathophysiology

Pancreatic ductal adenocarcinoma (PADC) is the most common histological form of pancreatic neoplasia, accounting for over 90% of all cases. It has a different genetic and molecular profile and natural history compared to other histological types, originating from the transformation of normal cells into low-grade and high-grade cells, and subsequently leading to the development of invasive adenocarcinomas [35]. The precursor lesions of pancreatic neoplasia can originate in the pancreatic ducts, with the emergence of pancreatic intraepithelial neoplasia (PanINs) in 85-90% of cases, or they can lead to mucinous cystic neoplasms (IPMNs) [36]. The progression from precursors to invasive cells occurs in several stages. KRAS mutations are present in most low-risk neoplasms and are considered the initiating factor of the pathology [37]. Subsequently, there is a loss of function of TP53 and SMAD4, with the histological expression being the appearance of high-grade lesions [35,38,39]. The transformation of normal cells into PanIN is achieved through the combined action of KRAS and the Sox9 gene, where a deletion of Sox9 leads to genomic stabilization, whereas its overexpression leads to accelerated progression toward PanIN [27]. Regarding the development of IPMNs, this occurs through the combined action of KRAS and the loss of PTEN activity [40].

The peritumoral stroma represents over 90% of pancreatic cancer when clinically evident and consists of accumulations of inflammatory cells, blood vessels, nerve endings, and also acellular components such as collagen, proteoglycans, hyaluronic acid, and fibronectin, with interstitial fluid in varying amounts [41]. Thus, through the interactions between the microenvironment and tumor cells, inhibition or proliferation of these cells can result [42]. Collagen is one of the main components of the extracellular matrix and interacts with pancreatic tumor cells through integrins A2B1, which control the motility of filopodia and their binding to proteins [43]. Type I collagen influences the level of E-cadherin and indirectly mediates the formation of the B-cadherin/E-cadherin complex, promoting the progression of pancreatic cancer and metastasis through the overexpression of N-cadherin by discoidin domain receptors (DDRs) [44]. Additionally, an increase in the synthesis of type I collagen is observed when PTEN activity is lost [45], with a particular topographical distribution, most often near malignant ducts of significant lengths and diameters [46], which differs from the distribution of collagen in chronic pancreatitis.

Another abundant element in the peritumoral stroma is hyaluronic acid, which promotes angiogenesis, proliferation, and migration of tumor cells, thus leading to accelerated disease progression [47]. This phenomenon may be due to the barrier function that the gel formed by hyaluronic acid with water can have for immune cells, simultaneously allowing the proliferation of neoplastic cells [48], associated with local immunosuppression through the transformation of macrophages into the protumoral M2 phenotype [49]. Additionally, malignant cells can degrade glycosaminoglycan chains through the hexosamine biosynthetic pathway via 6-phosphoamidotransferase 1 [50].

The repair of pancreatic tissue after an episode of acute pancreatitis relies on the interaction between epithelial and mesenchymal cells. Any alteration of the Hedgehog pathway can lead to the emergence of premalignant or malignant changes, especially if the oncogenes KRAS are also affected, as there is overexpression of these cellular phenomena by more than 50% compared to normal in pancreatic cancers [51].

Near malignant pancreatic tumor cells, in addition to the stroma, there are also cellular components such as immune cells and fibroblasts that can modify metabolic and genetic processes at this level through bidirectional interactions. Fibroblasts intervene in tumor development, homeostasis, and progression through their ability to synthesize extracellular matrix proteins, thereby increasing interstitial pressure and impeding the supply of nutrients and oxygen to the tissues, which can result in reduced cell proliferation at this level [52]. The activation of these cells in the tumor microenvironment leads to the release of CXCL12, which, through its interaction with the CXCR4 receptor, stimulates preneoplastic PanIN cells and their progression to invasive cancer [53]. Subsequently, the CXCL12 receptor is lost with the increase in invasiveness capacity; in aggressive forms, complete disappearance of this receptor occurs, indicating that other local factors (cytokines and growth factors) contribute to the emergence of aggressive forms with high metastasis rates [52].

Another cellular element abundantly observed in the peritumoral stroma is endothelial cells, which have the ability to form new blood vessels when neoplastic cells are subjected to local ischemic conditions. At the same time, they can serve as a source of hematogenous metastasis [54]. The expression of endothelial cell markers such as CD31 has been observed in substantial quantities on pancreatic tumor cells, and patients with elevated local levels had a better prognosis, as the receptors can stimulate immune genes such as CD4, GZMB, and CD8A, which will subsequently stimulate Toll-Like receptors, ultimately making them targets for immune cells to be eliminated [55]. When subjected to an ischemic environment and secondary low expression of CD31, neoplastic pancreatic cells lead to excessive synthesis of hypoxia-inducible factor 1α, which causes preferential binding of the interplay of long non-coding RNA-NUTF2P3-001 with miR-3923, resulting in overexpression of KRAS and subsequently enhanced proliferation and survival of neoplastic cells [56]. Increased levels of hypoxia-inducible factor 1α are a negative prognostic factor, alongside the complete absence of the gene from the genetic material of pancreatic cells [56].

Leukocytes are abundant cellular elements in pancreatic tumors, and the interactions between them and tumor cells can be modified by various agents to increase the chances of survival and healing, preventing micrometastasis and the risk of local recurrence [57]. The presence of neoplastic cells can elicit different reactions from the immune system. For example, infiltration of tissues with a small number of T cells indicates a lower rate of heterogeneity and a lesser antigenic stimulus, while a strong infiltrate, particularly with CD8+ cells, denotes a marked mutagenic status with lower survival, especially in patients undergoing surgical intervention [58]. In addition to CD8+ cells, peritumoral inflammatory foci also identify NK, B, macrophage, and granulocyte cells, each of which can influence disease development [56].

CD17+ Treg cells can lead to increased synthesis of IL-17, with elevated levels of this inflammatory marker found in peripheral blood. They can also influence the formation of preneoplastic cells by activating the mediator REG3-B in premalignant clones where the Kras gene is affected, which activates the gp130-JAK-STAT3 pathway, promoting metaplasia and the formation of PanIN [59]. Another effect of high levels of IL-17 is the stimulation of neutrophils, creating an environment that does not permit the activation of cytotoxic CD8+ cells due to the destruction of neutrophil extracellular traps, thus promoting local immunosuppression [60].

B cells can be a marker of poor prognosis in pancreatic cancer as they contribute to higher tumor growth rates and lower survival through various mechanisms. Their interaction with macrophages can induce M2 polarization, leading to decreased local inflammation and suppression of CD8+ cell activity, thereby stimulating tumor progression [61]. Furthermore, the presence of specific subsets of regulatory B cells, particularly B1 cells, which have a marked capacity to synthesize IL-12a and IL-35 (cytokines that inhibit local immune response) [62], can be present in the tumor microenvironment due to hypoxia leading to HIF1A deletion and excessive secretion of CXCL13 by fibroblasts, thus aiding in the development of neoplastic clones [63]. All these inflammatory cells, along with macrophages and myeloid cells, can be significantly influenced by the local microenvironment through the dynamic relationships between cellular and non-cellular elements, potentially leading to new therapeutic modalities [60].

Diagnosis

Numerous imaging methods can be used for the diagnosis of pancreatic cancer; the earlier it is detected, the better the survival rates compared to advanced stages [64]. The accuracy varies depending on the modality used, with computed tomography (CT) reaching up to 98%, followed by magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) at 86.55%. The changes that occur in pancreatic cancer are represented by indirect signs such as dilation and stenosis of the main pancreatic duct, with changes in the density of peripancreatic fat appearing in 42% of cases at stage 0, making it a potential marker for early diagnosis [65].

Endoscopic ultrasound can detect small lesions without using ionizing radiation and has the advantage of being able to obtain cytological samples. Compared to computed tomography, it detects pancreatic tumors smaller than 2 cm with rates of 95.2%, while thin-slice CT has an accuracy of 42.8%. Rates over 90% have been achieved using endoscopic ultrasound and fine-needle aspiration with histopathological results, with the ultrasound appearance of malignant or inflammatory lesions being hypoechoic. The use of contrast agents associated with ultrasound can better visualize the vascularization of the biliopancreatic tract, thus increasing the sensitivity of the imaging method in cases where cytological examination has not been performed [66].

Endoscopic retrograde cholangiopancreatography (ERCP) can allow for the collection of pancreatic fluid, stent placement, or biopsies. Compared to endoscopic ultrasound combined with fine-needle biopsy, it has good diagnostic rates but carries the risk of complications such as acute pancreatitis or contamination of pancreatic fluid by neoplastic cells upstream of the pancreas [65]. CT is useful for investigating suspicious lesions at the pancreatic level and can evaluate local and vascular invasion as well as metastatic disease [66].

Serological markers, in contrast to imaging methods, are minimally invasive, allowing for the collection of a single biological fluid that could theoretically diagnose pancreatic cancer quickly and cheaply. Currently, biological markers consist of glycolipids and proteins released from or by neoplastic cells, growth factors, DNA fragments, and circulating tumor cells [67]. CA19-9 is one of the most commonly used markers for monitoring and diagnostic suspicion of pancreatic cancer, with elevated levels observed in a range of benign diseases such as chronic pancreatitis or cholangitis [68,69]. Its sensitivity reaches up to 80%, but with low specificity. The association between CA19-9, CEA, CA 125 (with a sensitivity of 59% and specificity of up to 78%) [70] and CA 242 has led to a sensitivity of 90.4% and specificity of 93.8%, significantly higher than other markers taken individually [71].

Mucins are glycoproteins located on the surface of epithelial cells in the digestive tract, playing a role in increasing local acidity and reducing local infections through antimicrobial peptides, thereby enhancing local immunity [72]. In the case of pancreatic cancer, it has been observed that MUC5AC has the highest expression in premalignant lesions of the pancreas [73]. Locally, the effect of this glycoprotein is to stimulate dissemination and metastasis by activating ERK and VEGFR, as well as by reducing local immunity through inhibition of the TNF pathway and decreasing the amount of pro-inflammatory proteins CXCL8 [74]. The serum level of MUC5AC is associated not only with a poorer prognosis but also with a sensitivity of 82% and a specificity of 100% concerning the diagnosis of high-grade lesions [75].

Apolipoproteins are synthesized in the intestinal and hepatic levels and can function as ligands for membrane receptors or cofactors in various enzymatic reactions. APOA2, APOC1, APOC2, and APOE show significant dynamics in patients with pancreatic cancer [76]. Specifically, APOE has a sensitivity of 76.2% and a specificity of 71.4%, while APOA2 has a sensitivity of 51.3% and a specificity of 98.8% [77]. To increase the sensitivity and specificity in pancreatic cancer, it has been decided to combine these markers with traditional markers such as CA19-9, which can lead to detection 18 months earlier compared to conventional imaging diagnostic methods [78]. It has been observed that the use of multiple markers that intervene at different stages of neoplasia development can lead to higher rates of sensitivity and specificity. The combined use of CA19-9, serum IL-17 levels, low levels of immune checkpoint molecule B7-H1, and DR6 showed a sensitivity of 100% and a specificity of 90% in stage I pancreatic cancer [79].

Circulating tumor genetic material can serve as a diagnostic marker in pancreatic cancer, as tumor cells, DNA, and RNA fragments can be useful for the early detection of neoplastic processes in the pancreas [80]. The release of neoplastic cells into the bloodstream usually occurs in advanced cases. In pancreatic cancer, their presence correlates with a lower survival rate compared to patients where they are not identified, and the sensitivity of this method varies depending on the stage of the disease and the time elapsed since diagnosis, ranging from 25% to 100% [65]. Tumor stage and locoregional invasion do not closely correlate with the number of cells or their presence [81].

Circulating DNA can result from cellular necrosis or apoptosis and has a short plasma half-life, making it usable in the detection of pancreatic cancer through the mutations it harbors, particularly KRAS [82]. Isolation of the DNA strand of the KRAS gene at codon 12 is rarely detected in pancreatic cancer, but its association with other markers has resulted in a sensitivity of 64% and a specificity of 99.5% [83]. Exploring other circulating mutant genes involved in the pathogenesis of pancreatic cancer, such as

TP53, CDKN2A, and SMAD4, has led to greater diagnostic accuracy, achieving a sensitivity of 80% and a specificity of 100% in these cases. Notably, the length of base pairs in mutant KRAS strands varies with disease stage, where for early stages I and II, it does not exceed 85 base pairs, while for advanced stages, it reaches 150 base pairs [57].

Another genetic component that can be identified in the serum of patients with pancreatic cancer is represented by miRNA, which consists of small RNA strands 18-22 nucleotides long that mostly regulate gene expression post-transcriptionally [84]. The overexpression of miR-103 and miR-107, along with a reduced amount of miR-155, is associated with pancreatic cancer compared to normal individuals [85]. Furthermore, miR-25 could be a solution for early detection of this disease, showing a sensitivity of 75% and a specificity of 93% [86]. Unlike circulating DNA, miRNA is much more stable under conditions determined by the bloodstream, allowing for the identification of series of micro strands of genetic material. Thus, by using miR-20a, miR-21, miR-24, miR-25, miR-99a, miR-185, and miR-191, diagnostic accuracy rates of 83.6% can be achieved, significantly higher than using CA19-9 alone [87]. The use of multiple cellular RNA strands can lead to higher sensitivity and specificity rates of up to 85%, making it one of the most promising methods for the early diagnosis of pancreatic cancer [88].

Treatment

With a better understanding of disease development, a series of invasive and non-invasive methods have been developed to either prolong the lives of patients or, in some cases, achieve oncological cure. Surgical treatment is the only treatment that can lead to good survival rates, but its indications are often limited, as approximately 80% of cases are diagnosed as anatomically unresectable from the outset. The criteria for anatomical unresectability are represented by tumors that invade major vessels such as the celiac trunk, mesenteric vessels, common hepatic artery, or the mesenteric or portal veins [89]. Additionally, close contact with the superior mesenteric artery and vein for more than 180° also indicates unresectability [90]. If some of these characteristics are present, neoadjuvant therapy is necessary to reduce tumor size, increase rates of complete resection, and decrease lymph node and distant dissemination [91]. Surgical treatment varies depending on the tumor's location. For tumors located at the head of the pancreas or the uncinate process, a pancreaticoduodenectomy is required, with a 5-year survival rate of approximately 17% [92]. Better rates are obtained when the margin of resected tissue without tumor is greater than 1 mm, reaching up to 42% for the head of the pancreas and up to 53% for the tail and body of the pancreas. Therefore, to achieve the best results, the resection margins must be negative, and all infiltrated tissues along the celiac and superior mesenteric vessels must be freed. In cases of posterior invasion, the tissues anterior to the renal fascia must be cleaned [84].

Resection of the head of the pancreas can be performed through a medial-to-lateral approach, sectioning it at the formation of the portal vein. A disadvantage of this technique is the limited access to the superior mesenteric vessels; highlighting, dissecting, and freeing the superior mesenteric artery first provides the best visibility and postoperative results [93]. This can be approached from the posterior, anterior, medial, or superior aspect [94]. The tumor tissue is then dissected from the uncinate process posteriorly to anteriorly and laterally to medially. Due to the frequent invasion in the posteromedial area of the head of the pancreas and its relationship with the SMA (superior mesenteric artery), it is necessary to resect the periarterial adventitial tissue, the autonomic nerves, and all lymph nodes at this level [95]. To reduce the risk of local recurrence, which often occurs in the region of the interaortocaval lymph nodes, it is preferable to resect all tissue located between the celiac trunk, inferior mesenteric artery, and portal vein, but after complete mobilization of the SMA. Even though the surgical intervention may be prolonged, postoperative morbidity is not affected by this [96].

One of the complications of head pancreatic resection is the formation of a fistula [97], which varies in incidence between 5-15%, depending on the experience of the center and the patient's comorbidities (a history of smoking and the presence of ascites are associated with higher rates) [98]. To reduce the risk of this complication, it is preferable for the gastrojejunostomy to be performed antecolic while preserving the pyloric sphincter [99]. Minimally invasive approaches can be an alternative for head pancreatic resection, especially in tertiary centers with a high number of cases, as a significant learning curve, prolonged operating time, and often associated complications are necessary. Compared to traditional surgery, the mortality rate is lower, with complication rates of 16% and much lower blood loss [100]. Additionally, better results can be achieved with improved team efficiency regarding operating time and patient hospitalization, while maintaining similar rates concerning 5-year survival, number of resected lymph nodes, achieving negative resection margins, and complication rates [101].

Chemotherapy treatment is used for locally advanced or metastatic cases, primarily for palliative purposes. The FOLFIRINOX regimen, which combines 5-Fluorouracil, Folinic acid, Irinotecan, and Oxaliplatin, is commonly used, improving median survival without enhancing disease-free survival compared to gemcitabine alone, with a higher risk of hepatic, renal, metabolic, and hematological adverse reactions (with a high risk of leukopenia and neutropenia) [102]. Therefore, monotherapy with Gemcitabine is recommended for patients with an ECOG status greater than 2, and if progression is observed under treatment or relapse occurs,

it can be replaced with Irinotecan + 5-FU, which increases median survival by approximately 2 months for metastatic disease [103]. Another use of chemotherapy can be to reduce tumor sizes, decrease micrometastases, and achieve negative resection margins. Among all chosen regimens, FOLFIRINOX appears to be the most effective for borderline tumors and those with resectable potential, achieving complete resection rates of up to 33% with complete pathological response when the regimen was administered preoperatively [104]. For resectable tumors, the combination with external radiotherapy has shown increased disease-free survival (DFS) and R0 resection rates for patients who received prior chemoradiotherapy, but without a significant increase in overall survival [105].

Regarding borderline tumors, preoperative treatment is recommended first, and if these patients do not meet the criteria for oncological treatment, surgical results are unlikely to be favorable [106]. Better outcomes in terms of overall survival, disease-free survival, and R0 resection rates have been reported compared to patients who were initially operated on and subsequently received a chemotherapy regimen [105]. If arterial or venous vascular resection is necessary to achieve R0, there is no associated morbidity compared to the group of patients who did not receive preoperative treatment, demonstrating that the use of this treatment in borderline patients can enhance the effects of resection without a high risk of complications and additional mortality [107].

Immunotherapy treatment may be useful in managing patients with pancreatic tumors, achieving an increase in patient survival, but with rather poor results. The tumor microenvironment, rich in fibrosis and with a pronounced degree of hypoxia, can reduce the efficacy of these treatments, diminishing their immunomodulatory effect. For good results, agents that modify local conditions, inducing the death of neoplastic cells through immune mechanisms, are necessary [108].

KRAS is a metabolic pathway that can be influenced in the immunotherapeutic treatment of pancreatic cancer, both through direct action or through its effectors. The interaction with EGFR can be influenced by the administration of erlotinib + Gemcitabine, leading to better survival compared to gemcitabine alone in the case of advanced pancreatic cancer [109]. Another application concerning the KRAS gene involves the mutant G12C protein, which can be affected by the administration of Sotorasib, which inactivates it and inhibits the transmission of all subsequent oncogenic signals. Treatment administration in 8 patients resulted in the emergence of stable disease, while 1 experienced partial remission; a series of monoclonal antibodies targeting the mutant KRAS protein is currently under development [110].

The administration of an anti-KRAS mutant vaccine combined on the surface of a virus can be another way to attack the immune system against the tumor. Thus, in combination with gemcitabine, an increase in survival of up to 34.3 months was observed for patients who underwent surgical intervention, and at the same time, an increase in immune response of up to 95% was noted, evidenced by the enhanced synthesis of specific T cell proteins [108]. Other ways to target the KRAS pathway include RAS proteins through Vemurafenib and Dabrafenib, which have shown poor results as resistance to these molecules develops rapidly through various cellular mechanisms [111]. The MEK pathway is targeted by pimasertib, which in combination with gemcitabine achieved an increase in overall survival, although it was statistically insignificant and associated with a high risk of adverse reactions due to the phenotypic transformation of the cells [112].

Immunotherapeutic treatment can also attack the extracellular matrix rich in proteoglycans and hyaluronic acid. Inhibition of the TGF-beta pathway by galunisertib, in association with gemcitabine, led to increased overall survival (OS) and progression-free survival (PFS) for patients with unresectable pancreatic cancer [113]. Moreover, the combination with a monoclonal antibody targeting programmed death ligand 1 (Durvalumab) + galunisertib resulted in a 25% disease control rate and a disease response rate of 3.1% [114]. Hyaluronidase can cause deformation of the local stroma and decrease interstitial pressure, allowing for increased blood flow and better penetration of local chemotherapeutic treatment, an effect demonstrated in mice. The combination of such a compound capable of modifying the stroma with the classic FOLFIRINOX regimen did not yield better results; on the contrary, it resulted in higher metastasis rates associated with decreased OS and PFS due to the destruction of the barrier function that the microenvironment can have against the spread of tumor cells [115].

Stromal cells can be influenced by immunomodulatory treatment in pancreatic cancer through several pathways. Thus, through the binding of ibrutinib to Bruton's kinase, an anti-tumor response dependent on T cells was observed, which led to an increased anti-neoplastic response following gemcitabine administration [116]. Immune cells can also be influenced by immunotherapeutic treatment; through the CD47 receptor present in tumor clones, it acts as a blocker of phagocytosis. If inactivated by a monoclonal antibody (KWAR23), there is an increase in the ability of immune cells to phagocytize them, with increased activation of neutrophils and macrophages, associated with suppression of neoplastic cells [117]. Theoretical similar effects could also result from the administration of interferon 2a with stimulation of dendritic and NK cells through the IL-10 and INF-gamma pathways [118].

Conclusions

Although the discovery of the mechanism for transforming normal cells into neoplastic pancreatic cells has been achieved, inhibiting a single metabolic pathway

is not sufficient because there are compensatory mechanisms that favor the spread of abnormal clones. All of these are often accentuated and manipulated by the peritumoral stroma, which plays a role in isolating tumor cells on one hand, while on the other, it creates an environment in which they can thrive. Thus, the macroscopic response to these phenomena is the formation of an aggressive disease with a high capacity for metastasis, which can be difficult to detect in the early stages in absence of molecules with high specificity and sensibility. The most promising results regarding an early diagnosis are represented by the acquisition of a liquid biopsy in association with classical glycoprotein markers such as CA19.9 and CA125 and the best option for any patient with resecable pancreatic cancer is represented by surgical treatment which can be performed even in cases were loco-regional extension can be found if an adequate response to chemotherapy is found.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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