IOSR Journal Of Pharmacy
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 12, Issue 7 Series. I (July 2022), PP. 01-11 www.iosrphr.org

Pancreas Cancer: A Literary Review

Received 14 July 2022; Accepted 29 July 2022

Ana Paula Schneider Bruck , Bruna Fernandes da Silva ,Camila da Silva Senna Barroso, Isadora Cristina Teixeira Bono, Leticia Margon Manzini de Souza. Michelle Lima Garcez, Orlando Chiarelli Neto Espírito Santo University Center. Faculty of Medicine. Colatina (ES), Brazil . Emails: anasb1226@hotmail.com ; brufsilva@outlook.com ; camilabarrosocoutinho@hotmail.com ; isa_ctb@hotmail.com ; leticiamargon@hotmail.com Mi.lima.garcez@hotmail.com. ochiarelli@unesc.br.OrcidiD : https://orcid.org/0000-0003-1637-1642 ; OrcidiD : https://orcid.org/0000-0002-1424-452X; OrcidiD : https://orcid.org/0000-0002-2478-9371 ; OrcidiD : https://orcid.org/0000-0002-2323-5633 ; OrcidiD : https://orcid.org/0000-0002-3696-3103 ;OrcidiD: https://orcid.org/0000-0002-8685-1185; OrcidiD :https://orcid.org/0000-0002-8685-1185.
Corresponding author :**Orlando Chiarelli Neto**. Avenida Fioravante Rossi, 2930, Martineli . Colatina (ES), Brazil . CEP 29703-858. Phone (27) 99913-5181. Email:ochiarelli@unesc.br . OrcidiD : https://orcid.org/0000-0002-8685-1185

CONTRIBUTION OF EACH AUTHOR
The authors were divided as follows: the writing regarding the title, group components and affiliations, abstract, introduction, epidemiology, etiological agent and references, was under the responsibility of Camila da Silva Senna Barroso; the pathophysiology and prevention, on the other hand, was under the responsibility of Leticia Margon Manzini de Souza; the clinical picture, treatment and description of tables and figures was the responsibility of Bruna Fernandes da Silva; the diagnosis, prognosis and psychosocial aspects were the responsibility of Ana Paula Schneider Bruck ; the treatment was under the responsibility of Isadora Cristina Teixeira Bono, each of whom wrote her part, and , Orlando Chiarelli Neto and Michelle Lima Garcez , evaluated and approved each part written with the authors.

FINANCING SOURCE
There were no sources of funding.

CONFLICT OF INTEREST
There is no conflict of interest.

ABSTRACT
Introduction : Pancreatic cancer occurs as pancreatic adenocarcinoma, with a poor prognosis, which represents, in addition to pathophysiological changes, great psychosocial impacts on the patient's life, due to the fact that the disease presents itself, in most cases, late, making it difficult to early detection of tumor or pre-malignant tumors. Objective: To demonstrate updated data about the clinical aspects, diagnosis and treatments of the disease. **Method:** To obtain the data, 38 articles on the subject were used, researched in the main books and articles related to pancreatic cancer, from 2010 to 2021. Statistical were performed observing the equality between the understandings cited by each author, so that the thesis about each point of this article was confirmed **Results** : Mortality and incidence of pancreatic cancer are increasing rapidly in the world, having a direct relationship with individual characteristics, lifestyle and environment, and disease state. Although its early diagnosis is difficult, some forms of prevention can help prevent this cancer, such as smoking cessation, reducing alcohol intake, maintaining a healthy lifestyle and exercising. **Conclusion:** Pancreatic cancer is the twelfth most frequent cancer in the world, in which smoking has been established as an important risk factor and different genetic alterations have been observed in pancreatic neoplasms.
Keywords: pancreas ; cancer ; surgery .

I. INTRODUCTION

Pancreatic cancer is a malignant tumor, which often occurs as pancreatic adenocarcinoma, is characterized by its poor prognosis, due to the relative overall survival of 5 years[1] . Its incidence has increased dramatically in recent decades and is expected to continue to represent one of the leading causes of cancer-related mortality[2] . This occurs because the disease presents late, making early detection of the tumor or pre-

malignant tumors difficult and making it impossible to start treatment early. Despite improvement in surgical technique, chemotherapy and the introduction of neo-adjuvant chemoradiotherapy[1] . Early-stage surgical resection is currently the only effective treatment. Therefore, early diagnosis and surgical intervention represent the only effective means to improve outcomes in patients with pancreatic cancer[3] . It is important to identify risk factors, including lifestyle and inherited and acquired genetic factors, related to pancreatic cancer and its relationship with the development of the disease, in addition to observing their relationship with the lifestyle habits present in the most affected populations[2] . This review currently summarizes the epidemiological trends, risk factors, pathophysiological process, diagnosis and treatment of pancreatic cancer, to better understand this disease and enable an early diagnosis.

II. MATERIALS AND METHODS

This is a literature review, using a qualitative exploratory approach. The strategy of identification and selection of studies was the search for publications indexed in different platforms.

The following criteria were adopted for the selection of articles: all article categories; full-text articles available for review. Of the 38 articles obtained from 2010 to 2021, each one was carefully read, highlighting those that responded to the objective proposed by this study, in order to organize the data. Following the inclusion criteria, studies were selected for analysis, which are referenced in this text.

EPIDEMIOLOGY

Mortality and cancer incidence are rapidly increasing worldwide[2]. In the last two decades, the annual number of diagnosed pancreatic cancers has doubled. In 2017, there were 441,000 pancreatic cancers compared to the year 1990 with 196,000 cases worldwide[3]. According to the Global Cancer Observatory (GLOBOCAN) 2020, an estimated 495,773 patients were newly diagnosed with pancreatic cancer worldwide in 2020, ranking pancreatic cancer 12th among all malignant tumors [4]. The increase in pancreatic cancer is believed to be due to population growth and aging, as well as changes in the prevalence of major cancer risk factors, many of which are associated with socioeconomic development[2]. Therefore, the incidence and mortality from pancreatic cancer vary considerably around the world, with the highest rates being found in high-income countries[2], since a higher HDI was associated with increased incidence and mortality of pancreatic cancer [4].

There is a trend towards higher incidence rates in developed countries compared to developing countries, demonstrating that countries with a higher development index have higher incidences of pancreatic cancer in men and women [5] . Pancreatic cancer remains one of the cancers with the worst prognosis, with an overall 5-year survival, without much difference between high-income and low- and middle-income countries[2]. Low survival rates are, in part, attributed to the late stage at diagnosis in most cases, with only 20% of patients being diagnosed at the early stage of the disease.

RISK FACTORS

Risk factors for pancreatic cancer are related to individual characteristics, lifestyle and environment, and disease status[3] . Risk factors are classified as non-modifiable (age, sex, area, blood group, family history and genetic susceptibility, diabetes) and modifiable (intestinal microflora, smoking, alcohol, chronic pancreatitis [CP], obesity, dietetics, infection). Table [16] . Although it is estimated that 5 to 10% of pancreatic cancers have a hereditary component, the genetic basis for familial aggregation has not been identified in most cases. Sick individuals who have a known family history of pancreatic cancer in first-degree relatives have a relative risk of developing pancreatic cancer increased by a factor of 2, 6, and 30 in people with one, two, and three affected family members, respectively, compared to the general population [7] .

Table 1:

Risk Factors Associated with Pancreatic Cancer.
Non-Modifiable Risk Factors
Age
Sex
genetic factors
Diabetes
blood group
Modifiable Risk Factors
smoking
Human Microflora

Alcohol
Chronic Pancreatitis

Non-modifiable risk factors

Age

Pancreatic cancer mainly occurs in elderly individuals. It is extremely rare for young people under the age of 30 to develop the disease. Approximately 90% of newly diagnosed patients are over 55 years old, most are between 70 and 80 years old [1,3] .

Sex

The incidence of pancreatic cancer is lower in women than in men worldwide. The causes and mechanisms of sex differences, which may be related to genetic and lifestyle differences between men and women , require further exploration [1,3] .

Blood group

The ABO blood group antigen is present on the entire surface of red blood cells. Individuals with blood types A, B and AB are at higher risk compared to blood type O. Recent studies have shown that antigens affect the risk of pancreatic cancer, that is, the gene that encodes blood group plays a direct role in tumorigenesis and malignancy.

Genetic factors

In recent years, studies have found that pancreatic cancer has a clear family base, and a family history greatly increases the risk, mainly through genetic and acquired genetic mutations. More than 80% of pancreatic cancers are due to sporadic mutations, and a small number of cases are caused by specific genetic mutations. Approximately 5 to 10% of patients with pancreatic cancer have a family history of pancreatic cancer.

Familial risk increases exponentially with increasing number of first-degree relatives. Currently, chromosomal aberrations at loci13q22, 15q14,17,18 6p25, 12p11, 7q36, 21q21, 5p13, 21q22, 22q13 and 10q26 have been discovered by scientists from Japan and China. In the largest genomic collection in Europe, 7p12, 1p36, 8q21, 17q12 and 18q21.32 deletions of PC susceptibility chromosomal targets were identified. Point mutations3,7 in K-RAS, CDKN2A (P16), TP53, SMAD4, frequently involved in pancreatic cancer [1,3] .

Diabetes

A significantly increased risk of developing pancreatic cancer in people with diabetes is confirmed. In type 1 diabetes, the risk increases 5 to 10 times in patients with a disease duration of more than 10 years. People with diabetes diagnosed with the disease more than 20 years ago are at increased risk for pancreatic cancer. Compared with patients without diabetes, newly diagnosed patients with diabetes have an almost 7-fold increased risk.

In pancreatic cancer patients, blood glucose and glycated hemoglobin (HbA1c) levels increased significantly 1 month before the diagnosis of diabetes. Therefore, HbA1c is expected to be a potential biomarker to predict PC [1,3] .

Modifiable risk factors

Human Microflora

The human microbiota is composed of a variety of organisms, including bacteria, fungi, viruses and protozoa. Studies have shown that the occurrence, development and prognosis of pancreatic cancer are closely related to the human microbiota, as are some hepatitis and bile viruses [1,3] .

Another factor is related to microbial secondary products such as fatty acids, lipoteichoic acid (LTA) and short-chain fatty acids (SCFAs), which play important roles in cancer cell growth, and microbial toxins and virulence can cause chronic inflammation. , and can also destroy cellular DNA[1].

Microbiota dysbiosis , due to dysregulation of the human microbial system, by factors such as diet, sex, genetic hormones, bile acids and infectious diseases, leads to reduced microbial diversity in the intestine and other organs of the body, is also related to genetic mutations. and ultimately affects the normal immune system[1].

Studies have shown that periodontal disease and tooth loss are associated with a 50-70% increased risk of pancreatic cancer, that is, a future risk of pancreatic cancer. The mechanism underlying this association is unclear and questions remain as to whether there is a direct causal correlation [1,2] .

Smoke

Among the factors associated with pancreatic cancer, smoking is the most important modifiable factor, as it is closely associated with the occurrence and development of pancreatic cancer [1,3] .

Results of one study showed that current smokers had a 37% greater risk of pancreatic cancer than nonsmokers (RR, 1.37; 95% CI, 1.11–1.69) and that pancreatic cancer risks were significantly higher in former smokers (RR, 1.8; 95% CI, 1.7–1.9) than in nonsmokers (RR, 1.2; 95% CI, 1.1–1 ,two). Another factor is that the higher the amount of smoking, the greater the risk of pancreatic cancer[3].

Alcohol

Population studies showed that alcohol consumption increased the risk of pancreatic cancer [8] . Another study found that the risk of disease was significantly higher in people who drank more than 30g a day (RR: 1.22, 95% confidence interval (CI): 1.03-1.45). There was also a meta-analysis that found that low and moderate alcohol consumption was not associated with risk of pancreatic cancer[1].

Chronic pancreatitis

There is growing evidence that pancreatitis, a progressive inflammatory state of the pancreas that causes pancreatic fibrosis and loss of islet cells, is an independent risk factor for pancreatic cancer. Pancreatitis can also disrupt the endoplasmic reticulum, mitochondria and lysosomal autophagy systems of pancreatic cells and can lead to cellular DNA damage, chromosomal mutations and oncogene activation[1].

PATHOPHYSIOLOGY

There are two types of precursor lesions, intraductal papillary mucinous neoplasm and mucinous cystic neoplasm . Mucinous cystic neoplasm occurs more in women after 40 years, and is more common in the body and tail of the pancreas. The intraductal papillary mucinous neoplasm affects both men and women and is more frequent in the pancreatic head. The evolution occurs from pre-invasive intraepithelial neoplasia to invasive ductal adenocarcinoma [9.]

Pancreatic cancer happens due to the accumulation of mutated genes. The lesion called pancreatic intraepithelial neoplasia is the best characterized histological lesion precursor of pancreatic cancer. The progression from minimally dysplastic epithelium (pancreatic intraepithelial neoplasia grades 1A and 1B) to more severe dysplasia (pancreatic intraepithelial neoplasia grades 2 and 3) and finally to invasive carcinoma parallels the multiple accumulation of mutations that activate the KRAS2 oncogene , and inactivation of the CDKN2A tumor suppressor gene (which encodes the cyclin -dependent kinase 4 inhibitor [INK4A]), and inactivation of the tumor suppressor, which is TP53, also occurs. Other premalignant lesions of the pancreas are mucinous intrapancreatic neoplasm and mucinous cystic neoplasm. Most patients with pancreatic cancer carry one or more of these defective genes [9] .

Ninety percent of tumors have activating mutations in the KRAS2 oncogene . Transcription of the mutant KRAS gene produces an abnormal Ras protein that is “blocked” in shape, resulting in aberrant activation of proliferative and survival signaling pathways. Similarly, 95% of tumors have inactivation of the CDKN2A gene, with the resulting loss of the p16 protein (a regulator of the G1-S transition of the cell cycle) and a corresponding increase in cell proliferation. TP53 is abnormal in 50 to 75% of tumors, allowing cells to bypass DNA damage and bypass apoptotic checkpoints and signals, thus contributing to genomic instability [9] .

DPC4 is lost in approximately 50% of pancreatic cancers, resulting in aberrant signaling by the transforming growth factor β (TGF-β) cell surface receptor. The basis of pancreatic cancer is extremely complex and heterogeneous [9] .

The development of DM in patients with pancreatic cancer is likely secondary to a combination of factors that lead to a marked decline in pancreatic β-cell function and profound peripheral insulin resistance. Patients with advanced CP have many of the metabolic abnormalities seen in type 2 DM, including glucose intolerance, increased hepatic glucose production, and insulin resistance. There is an increasingly recognized interaction of drugs commonly used for DM as having an anticancer role that may further influence the outcome of pancreatic cancer [4] .

(miRNAs) are small non-coding RNA molecules that bind to messenger RNA causing its inhibition or degradation. By inhibiting the expression of tumor suppressor genes or promoting the expression of proto-oncogenes , aberrant miRNA expression can promote carcinogenesis in human cancers. However, miR-320a was upregulated in pancreatic cancer cells resistant to 5-fluorouracil (5-FU), which is a chemotherapy drug, and that miR-320a could promote the proliferation, migration and invasion of pancreatic cancer cells, contributing to increased resistance to 5-FU. This suggests that miR-320a may serve as a target for pancreatic cancer therapy. Therefore, identifying miRNAs that have key roles in the drug resistance process in pancreatic cancer and understanding the role of the specific molecule is useful for us to understand the pancreatic cancer chemotherapy drug resistance process in the future [10] .

PREVENTION

There is no known way to prevent this type of cancer. But some preventive measures can be adopted to try to reduce the incidence, such as smoking cessation, both actively and passively, reducing the intake of alcoholic beverages, maintaining a healthy lifestyle, with a balanced diet, always including fruits and vegetables, avoid foods rich in sugars and carbohydrates, as they can raise the patient's blood glucose; practice physical exercises of at least 150 minutes per week[2].

For people undergoing surgery for gastric or duodenal ulcers, or cholecystectomy , patients who have chronic pancreatitis or diabetes mellitus are recommended to undergo periodic examinations to assess pancreatic function, because these individuals are more likely to develop pancreatic cancer, as well as for those with a family history of cancer [11] .

CLINICAL CONDITION

Pancreatic cancer is often diagnosed at an advanced stage, when the cancer has metastasized to distant organs such as the liver, lung, lymph node, and peritoneal cavity. Unfortunately, due to the clinical presentation, 85% of the tumors are unresectable , which translates into a poor prognosis and high mortality in the absence of effective chemotherapy and radiotherapy[2].

Those who develop symptoms often have nonspecific complaints such as epigastric or back pain, nausea, bloating, abdominal fullness, or change in stool consistency, which are symptoms usually attributed to alternative, benign causes, which can delay diagnosis. Clinical features that occur most frequently at diagnosis include abdominal pain, abnormal liver function tests, jaundice, new-onset diabetes, dyspepsia, nausea or vomiting, back pain, and weight loss. Approximately 60-70% of pancreatic tumors arise from the pancreatic head or neck and are more likely to cause biliary obstruction, leading to the classic presentation of a patient with painless jaundice. Pancreatic body tumors tend to invade local vascular structures, including the celiac, hepatic, and superior mesenteric vessels, in addition to the portal vein, and are more likely to cause back pain at presentation [9] .

Somatic pain arises from local invasion and metastasis to the peritoneum, retroperitoneum, and surrounding bones, while visceral pain arises from infiltration of tissues adjacent to organs such as the liver and the accumulation of ascites in advanced-stage patients. Specifically, pain resulting from metastases to the liver and bile duct presents problems due to high incidence rates in patients with pancreatic cancer [12] .

Anorexia, weight loss, and depletion of lean body mass are typical presenting features of pancreatic cancer. Both the severity of these events and the consequent changes in body composition have been correlated with the stage of the disease and unfavorable oncological outcomes. Sarcopenia and sarcopenic obesity are associated with increased postoperative morbidity, impaired adherence to adjuvant chemotherapy and reduced long-term survival [13] .

Recent studies have revealed that obesity and pancreatic cancer are strongly associated. Insulin resistance is a hallmark of T2DM, where insulin fails to trigger adequate glucose uptake, leading to accumulation of circulatory glucose as well as increased insulin levels. However, new-onset diabetic patients who develop diabetes at an older age, accompanied by weight loss and excessive exocrine damage, are at greater risk of the disease than the long-term diabetic population [2,1] .

Hyperinsulinemia causes an increase in insulin growth factor (IGF)-1 which, upon binding to its receptor, or insulin-like growth factor receptor (IGFR), activates the mTOR , PI3K, and MAPK pathways. These are well-known pathways in cancer biology that promote cell proliferation and angiogenesis and inhibit apoptosis, thus fueling cancer growth. The increase in food consumption by obese individuals, often combined with poor eating habits, also increases exposure to carcinogenic agents [14] .

DIAGNOSIS

Pancreatic cancer has very high mortality rates, and this fact is closely related to its pathophysiology, very late diagnoses and lack of standardized guidelines [5] . The diagnosis of pancreatic cancer is very difficult to be made early, and this is due to the absence of non-specific signs or symptoms that patients present and also to the close proximity that this tumor often has with blood vessels of great importance to the body. , thus making metastasis occur more easily and quickly[1]. Less than 10% of pancreatic cancers are found to be in the local stage at the time of diagnosis. Due to its location and stage of the tumor, most of the time it is not surgically resectable, which ends up complicating its prognosis even more, since surgical resection is the only known way to cure pancreatic cancer [15] .

directed anamnesis and physical examination , then laboratory and imaging tests will be performed. In the anamnesis, it should be asked about the complete clinical picture, including information about typical signs and symptoms of the diseases to observe if the patient has any of them, investigate about risk factors, family history and other diseases, since the physical examination should be performed . complete and focusing mainly on the abdomen to try to perceive any masses or accumulation of liquids [16] .

Imaging tests are extremely important for early diagnosis, differential diagnosis, screening, monitoring of the patient's evolution and prognosis. Regarding each test that is used to make the diagnosis. Table 2 [17] :

- Computed tomography: it is a non-invasive exam, in many guidelines it is used as a method of first choice, it has better validity for the imaging of patients with pancreatic cancer, it has wide images that allow the exam to cover the local and distant disease, and also this method has a sensitivity of 89% and a specificity of 90%. However, it presents a problem when it comes to radiation to which the patient is exposed and the use of contrast, as there is a risk of the patient suffering nephrotoxicity [5] . On the other hand, positron emission

tomography is not widely used to diagnose cancer, however, it is indicated for patients with occult metastatic disease [15].

- Magnetic resonance imaging: this exam has little availability and high cost, being the second line of diagnostic option. computerized to make the diagnosis more accurate [5].
- Endoscopic ultrasound: it is a safe procedure, without much discomfort for the patient, it is more used for lesions of smaller diameter and is often used because it has the benefit of being able to make a puncture to be carried out a cytopathological exam or when other exams are needed. failed to obtain a biopsy of the lesion [5]. This method has an advantage over others, as it does not use ionizing radiation or contrast; however, it has the disadvantage that this method cannot accurately distinguish between carcinomas and other diseases without a cytological examination [17].
- Elastography : Currently, a new means of diagnosis has been developed, which is real-time elastography , in which an evaluation of tissue elasticity is carried out using ultrasound and it has been useful to evaluate tumors and to detect whether the lesion is benign or not. malignant [17].

It still does not have serum tumor markers that are completely effective for the diagnosis of pancreatic cancer. However, CA19-9 is considered a biomarker of pancreatic cancer, it is used to monitor the response in the patient's body to systemic treatment, and is also used as a marker for disease recurrence[1].

Often CEA, CA125 and CA242 can be used together to make the diagnosis and together all these markers have greater sensitivity and specificity for the diagnosis [17]. On the other hand, the concentration levels of CA-19 are related to the type of prognosis of the patient and CEA and CA125 may be elevated in patients with this type of cancer, however, only the markers are not fully effective to make the diagnosis of cancer. of pancreas [15].

The differential diagnosis of pancreatic cancer can be made with some diseases, mainly those involving the gastrointestinal system, such as acute and chronic pancreatitis, tumors and bile duct stenosis, gastric cancer and ulcer, cholangitis , cholecystitis , cholelithiasis [5].

	Benefits	**Disadvantages**
Tomography computerized	- Non-invasive method; -First choice for the diagnosis (according to a large part of the guidelines); - Widely available; - Sensitivity 89%; - 90% specificity	- Use of contrast; - Nephrotoxicity
MRI	- Second choice for the diagnosis; - Useful for patients with contrast sensitivity and renal impairment; - Use of CT+RM for greater accuracy in diagnosis; - Sensitivity and 89% specificity	- Low availability and high cost
ultrasound	- Safe; - Slightly uncomfortable method ; - Used for injuries smallest diameter; - Possibility of image orientation to carry out cytopathological examination ; - Does not use radiation ionizing or contrasting; - More modern method	- Low specificity for identification between carcinoma and others illnesses

COMPLEMENTARY EXAMS FOR DIAGNOSIS OF CANCER OF THE PANCREAS.

Table 2

PROGNOSIS

Pancreatic cancer occupies the seventh place in the ranking of neoplasms that cause the highest mortality in the world. This type of cancer has a very low survival rate, it is estimated that the five-year survival

of pancreatic cancer is only 5%. Its very complicated prognosis is due to the rapid dissemination in the lymphatic system and to other organs and also due to its nonspecific symptoms that make it difficult to discover this neoplasm at an earlier and less aggressive stage [18].

It is estimated that more than 90% of patients were diagnosed in stages III and IV. The best way to improve the prognosis of this disease is to make the diagnosis early, for that the signs and symptoms suggestive of this condition must be understood by health professionals and those who are at high risk for this neoplasm should undergo exams with a certain frequency to be detected, if they have the disease [19].

It was seen about the relationship of interleukins with metastasis, angiogenesis and the poor prognosis of pancreatic cancer, and it was concluded that only the levels of IL-6, IL-8 and IL-10 were related to survival time. of patients with this type of cancer, since patients with high expression of these three interleukins ended up having a shorter survival time compared to patients with low expression [20].

Regarding tumor markers and prognosis, CA19-9 is commonly used as a significant prognostic factor for the evaluation of therapeutic effects, surveillance of metastases and prediction of survival in patients with advanced stage pancreatic cancer [17].

Cytotoxic T lymphocytes play a role in eliminating tumor cells that expose tumor-specific antigens. When it has a higher density of CD8 + T cells in tumor tissues, it is related to the expression of cytotoxicity genes and is usually associated with prolonged survival of patients with pancreatic cancer and those patients with high infiltration of cytotoxic T cells have a better response to chemotherapies [21].

Among pancreatic cancer subtypes, squamous, QM-PDA (quasi-mesenchymal) and basal- like were the most associated with the worst prognosis. The prognosis of pancreatic cancer is not only related to the characteristics of the tumor, but it is also related to the patient's health status and how the treatment was performed and the response that the patient obtains on this treatment [22]. Surgery is known as the only cure method, however, even so, survival is low, being 12 months after this surgical removal [18].

TREATMENT

Little progress has been made in improving the survival rate of pancreatic cancer, mainly due to the fact that it often goes undetected until late stages. For pancreatic cancer that can be diagnosed at an early stage (stage IA and IB), the survival rate is improved with surgery and chemotherapy. Pancreaticoduodenectomy (Whipple procedure) , distal or total pancreatectomy are the surgical options for resection of pancreatic cancer, depending on the anatomical location of the tumor [23,1].

Pancreatic head tumors are typically resected with a pancreatoduodenectomy (Whipple procedure) that includes resection of the pancreatic head, duodenum, proximal jejunum, common bile duct, gallbladder, and a segment of the stomach. Tumors located in the body or tail of the pancreas can be treated with distal pancreatectomy , often combined with splenectomy. Vascular resections at the time of tumor resection are often performed to obtain negative surgical margins [9].

Chemotherapy:

Pancreatic cancer is not sensitive to most current chemotherapy drugs. More than 80% of patients with pancreatic cancer are diagnosed when the lesion is not suitable for operation. Therefore, it is urgent to develop an effective drug with fewer side effects and toxicity to treat patients with pancreatic cancer [24]. The current standard of care is initial resection and adjuvant chemotherapy with gemcitabine or a combination of chemotherapy. A modified protocol of FOLFIRINOX (mFOLFIRINOX) demonstrated tremendous efficacy in the adjuvant setting compared to Gemcitabine alone with a median disease-free survival (mDFS) of 21.6 months compared to 12.8 months [9,25].

Gemcitabine (2 ',2'-difluorodeoxycytidine) (GEM), although very promising for the treatment of cancer, has a short half-life in the systemic circulation. To improve its effectiveness, frequent administration of high doses of GEM is required, which can cause myelosuppression and hepato and nephrotoxicity . There are many reports demonstrating that the antitumor efficacy of gemcitabine was significantly improved when it was administered together with chemotherapeutic agents such as paclitaxel , doxorubicin or retinoic acid using nanocarriers [26].

Poly (ADP-ribose) polymerase (PARP) inhibitors target tumor cells with homologous recombination repair (HRR) deficiency based on the concept of synthetic lethality. The most prominent target gene is BRCA. PARP inhibitors can trap the PARP-1 protein in a single-strand break/DNA lesion and interrupt its catalytic cycle, leading to replication fork progression and consequent double-strand break. For tumor cells with BRCA mutations, loss of HRR would result in cell death. Pancreatic cancer has also been reported to have a strong relationship with BRCA gene mutations, which indicates that pancreatic cancer patients may benefit from PARP [27] inhibitors.

Immunotherapy:

Immunotherapy modulates the host's immune response to tumor associated antigens (TAAs), eradicates cancer cells by reducing the host's tolerance to TAAs , and provides short- and long-term protection against disease. Passive immunotherapies, such as monoclonal antibodies or therapies based on engineered T cells, directly target tumor cells, recognizing TAA [8] . Tissue factor (TF) overexpression has been associated with increased tumor growth, angiogenesis and metastasis in many malignancies, including pancreatic cancer [28] . T cells are collected from the patient and genetically modified to recognize the target. They are then expanded ex vivo and then reinfused into the patient, which is a laborious and time-consuming therapy [29] .

Mucin1 (MUC1) is a highly glycosylated transmembrane protein that plays a crucial role in lubricating and protecting normal epithelial cells. However, MUC1 has emerged as a potential target for cancer therapy because it is overexpressed and works in many types of cancer. Recently, a monoclonal antibody (the anti-hMUC1 antibody) specific for the extracellular region of the MUC1 subunit MUC1-C was produced to assess the utility of using anti-MUC1 antibodies in pancreatic cancer models. Anti-hMUC1 antibody suppressed epidermal growth factor (EGF)-mediated extracellular signal-regulated kinase (ERK) phosphorylation and cyclin D1 expression. When anti-hMUC1 antibody was injected into a mouse xenograft model and screened using an in vivo imaging system, we observed that anti-hMUC1 antibody was localized to pancreatic tumors expressing MUC1. Importantly, the anti-hMUC1 monoclonal antibody suppressed pancreatic tumor growth in mice [23] .

Betulinic acid , an important natural product extracted from the date seed, has multiple biological activities, such as antimalarial, anti-inflammatory and anti-HIV . It can regulate the expression of inflammatory cytokines to improve inflammation. Broad biological activities against different types of cancer have been recently reported. Betulinic acid can suppress pancreatic cancer both in vitro and in vivo in a dose-dependent manner, which expands the anticancer class of betulinic acid . Furthermore, recent studies show the potential mechanism by which betulinic acid inhibits pancreatic cancer and we found that it induces apoptosis specifically through targeting mTOR signaling rather than Nrf2 or JAK2. These findings indicate that betulinic acid acts as a potential and valuable anticancer agent for pancreatic cancer and indicate the specific molecular target [24,26] .

Online adaptive magnetic resonance guided radiotherapy for pancreatic cancer

Conflicting results on the benefit of chemotherapy, radiotherapy (RT) and their combination (CRT) in pancreatic cancer have been reported in the literature: the LAP07 randomized clinical trial did not observe a significant difference in overall survival with CRT compared with chemotherapy alone, while the GERCOR study suggested that sequential CRT could improve the survival of patients with pancreatic cancer compared with chemotherapy alone; also the EasternCooperativeOncologyGroup (ECOG) study demonstrated the superiority of the gemcitabine plus radiotherapy arm compared to gemcitabine alone, even though the rate of severe toxicity was higher. One of the most promising delivery techniques is represented by stereotactic body radiotherapy (SBRT), considered as a unique approach or in combination with other therapeutic approaches. The most significant advantage offered by the innovative MR-guided radiotherapy (MRgRT) approach is represented by the superior soft tissue contrast offered by MR, which allows for more accurate identification of therapy volumes relative to what is achievable using [30] ° CT imaging.

PSYCHOSOCIAL ASPECTS

Depression occurs in around 15 to 30% of patients who have cancer, a rate that is much higher than compared to the general population, however, this rate in patients with pancreatic cancer ends up rising to 50 to 78%. and many of these also present anxiety concomitantly with depression. Cancer patients and their families often end up with a high rate of depression and anxiety, as they are very exposed to factors such as physical, psychological and financial stress. It is believed that depression may also be related to underlying metabolic causes for which the exact mechanism is not yet known, but which are linked to neoplasia [31] .

Depression was more prevalent in Caucasians and patients aged between 18 and 65 years and it was also seen that patients who developed depression after the discovery of the disease had a higher mortality [32] .

Whenever diagnosed, the patient with pancreatic cancer with depression or anxiety should be referred for follow-up with mental health professionals and an adjuvant treatment with antidepressant therapy should be performed, because, if left untreated, it will interfere and greatly worsen the prognosis and the patient's oncological condition [32] .

III. RESULTS

According to the data obtained, it is clear that pancreatic cancer is very common among cancer cases in the world, with a significant increase in the last two decades, in which 85% of tumors are unresectable , which translates into a poor prognosis and high mortality in the absence of effective chemotherapy and radiation therapy .

These data are mainly associated with society's life habits, due to the fact that there has been an increase in smokers and alcoholic beverages, as well as the population's lack of concern for leading a healthy

life, both in terms of food and physical activities. , which can be aggravated by age, sex, obesity and genetic factors, all of which are considered risk factors.

In addition to the possible causes of pancreatic cancer, it is noted that its pathophysiology is associated with two types of precursor lesions, intraductal papillary mucinous neoplasm and mucinous cystic neoplasm , each with its own particularities, as well as the accumulation of genes. that have mutated, where ninety percent of tumors have activating mutations in the KRAS2 oncogene , and patients with advanced CP have many of the metabolic abnormalities seen in type 2 DM, including glucose intolerance, increased hepatic glucose production, and resistance to insulin.

Considering the pathophysiology of pancreatic cancer, and its main causes, it is observed that possible preventions would be related to improvements in life habits, such as better diet, physical activity, lower alcohol intake, avoiding smoking, and performing periodic examinations when there are risk factors in the family, thus making this type of cancer have an early prognosis, so that its treatment can be satisfactory.

However, it appears that it is very difficult to make an early diagnosis of pancreatic cancer, and this is due to the absence of nonspecific signs or symptoms that patients present, as well as the close proximity that this tumor often has with blood vessels . of great importance to the body, making metastasis occur more easily and quickly.

In order to have an early and differential diagnosis, as well as the proper follow-up of the patient's evolution, it is extremely important to use imaging tests, including magnetic resonance imaging, endoscopic ultrasonography, computed tomography and elastography , CT is the first choice for diagnosis .

With regard to prognosis, it is estimated that more than 90% of patients were diagnosed in stages III and IV, as well as a relationship of interleukins with metastasis, angiogenesis and poor prognosis of pancreatic cancer, reaching if the conclusion that only the levels of IL-6, IL-8 and IL-10 were related to the survival time of patients with this type of cancer, as patients with high expression of these three interleukins ended up having a shorter survival time , in relation to patients with low expression.

Considering that pancreatic cancer is most often discovered late, the current standard of treatment is initial resection and adjuvant chemotherapy with gemcitabine or a combination of chemotherapy, as results are still conflicting in the literature. on the benefit of chemotherapy, radiation therapy (RT) and their combination (CRT) in pancreatic cancer.

IV. DISCUSSION

The data obtained may represent a possible pressure on people's lives, especially in the socioeconomic context, which leads them to discount anxiety and stress in the increased intake of harmful foods, as well as in the increase in alcohol consumption and smoking. This factor can be correlated with the COVID-19 pandemic, for example, which affected the entire world in the last two years, and caused people to feel trapped, who discounted suffering in harmful habits of life.

In view of all the data obtained and specified above, in the topic of results, it is possible to verify that great advances still need to be made regarding the prognosis and treatment of pancreatic cancer, considering that, due to human conditions, the diagnosis occurs, in most cases, late, thus causing their treatment not to have a quick and immediate response for the patient, influencing their physical and emotional life, which even causes an increase in cases of depression in patients with this type of cancer.

However, one way for all people to prevent this type of cancer is to adopt healthy eating habits, physical exercise, avoid alcohol and smoking, as well as keep preventive exams up to date, especially people who have family members who already had the disease.

V. CONCLUSION

Pancreatic cancer is the twelfth most frequent cancer in the world, in the last two decades the annual number of diagnosed pancreatic cancers has doubled. Smoking has been clearly established as an important risk factor affecting the carcinogenesis of pancreatic carcinoma. Bad lifestyle habits have also been linked to pancreatic cancer. Different genetic alterations have been observed in pancreatic neoplasms.

Typical symptoms of pancreatic cancer are abdominal pain, jaundice, new-onset diabetes, dyspepsia, nausea or vomiting, back pain, and weight loss. This type of cancer has a very low survival rate, thus being considered one of the worst prognosis neoplasms. Its poor prognosis is due to the rapid spread to the lymphatic system and other organs and is also due to its nonspecific symptoms that make it difficult to discover this neoplasm at an earlier and less aggressive stage.

Imaging tests are important for early diagnosis, differential diagnosis, screening, follow-up of the patient's evolution and prognosis, and computed tomography is often the first choice. Regarding the treatment of pancreatic cancer, surgery remains the main factor in improving survival, however, as options there are immunotherapy, chemotherapy and radiotherapy guided by magnetic resonance, the latter still under study.

REFERENCES

[1]. McCain et al. Pancreatic cancer: **A review of clinical diagnosis, epidemiology, treatment and outcomes** . World Journal of Gastroenterology.DOI: 10.3748 / wjg.v24.i 43.4846 . 2018

[2]. Klein. **APEpidemiology of pancreatic cancer: understanding the role of lifestyle and hereditary risk factors** . Nature Reviews Gastroenterology & Hepatology. DOI https://doi.org/10.1038/s41575-021-00457-x. 2021 _

[3]. Cai et al **. Advances in theepidemiologyofpancreaticcancer : Trends, riskfactors , screening, andprognosis** https://doi.org/10.1016/j.canlet.2021.06.027 . 021 Elsevier BV Allrightsreserved . 2021.

[4]. Beg,Muhammad et al. **Impact of Diabetes Mellitus on the Outcome of Pancreatic Cancer** . Plosone.DOIhttps://doi.org/10.1371/journal.pone.0098511 https://doi.org/10.1371/journal.pone.0098511. _ 2014.

[5]. Lulu Zhang, Santosh Sanagapalli , and Alina Stoita . **Challenges in diagnosis of pancreatic cancer** . World Journal of Gastroenterology. DOI: https:// 10.3748/ https://dx.doi.org/10.3748%2Fwjg.v24.i19.2047wjg.v24.i https://dx.doi.org/10.3748%2Fwjg.v24.i19.204719.2047 . 2018

[6]. ZhiYu Zhao1, and Wei Liu, **Pancreatic Cancer: A Review of Risk Factors, Diagnosis, and Treatment.** DOI : 10.1177/1533033820962117. 2020

[7]. David P. Ryan, MD, Theodore S. Hong, MD, and Nabeel Bardeesy , Ph.D. , **Pancreatic Adenocarcinoma. The New England Journal of Medicine – Review article** . DOI: 10.1056/NEJMra1404198. 2014.

[8]. Banerjee, Kasturi et al. **Emerging trends in the immunotherapy of pancreatic cancer . Cancer Letters** . DOI: https://doi.org/10.1016/j.canlet.2017.12.012 . 28 March 2018.

[9]. Manuel Hidalgo and MD **Pancreatic Cancer** . The new England journal of medicine. DOI:DOI : 10.1056/NEJMra0901557 . 2010.

[10]. WANG, WEIBIN et al. **MicroRNA -320a promotes 5-FU resistance in human pancreatic cancer cells** .Nature.2021.DOI: https://doi.org/10.1038/srep27641 .

[11]. Nobeschi , Leandro; Bernardes, Wilson; Favero , Nilze . **Diagnosis and prevention of pancreatic cancer** . Essays and Science: Biological, Agricultural and Health Sciences. 2012. ISSN: 1415-6938.

[12]. INES LOHSE and SHAUN P. BROTHERS. **Pathogenesis and Treatment of Pancreatic Cancer Related Pain** . Anticancer Research April, 40 (4) 1789-1796 ;DOI : https://doi.org/10.21873/anticanres.14133. 2020 _

[13]. Sandini M, Patio M, Ferrone CR, et al. **Association between changes in body composition and neoadjuvant treatment for pancreatic cancer** s. JAMA Surg;153(9):809–815. doi:10.1001/jamasurg.2018.0979. 2018

[14]. Rawla , P., Thandra , K. & Sunkara, T. **Pancreatic cancer and obesity: epidemiology, mechanism, and preventive strategies** . ClinJGastroenterol 12, 285–291.DOI: https://doi.org/10.1007/s12328-019-00953-3. 2019 _

[15]. MIZRAHI, D. Jonathan; Surana, Rishi; Valle, Juan W; Shrof , Rachna T. **Pancreatic cancer** , The Lancet, 27, jun. DOI:https ://doi.org/10.1016/S0140-6736(20)30974-0. 2020

[16]. INCA, **Pancreatic Cancer,** 2019.

[17]. You et al. **Early screening and diagnosis strategies of pancreatic cancer: a comprehensive review** . CancerCommon (London). DOI: 10.1002/cac2.12204. 2021.

[18]. Santos et al. **Clinical-Epidemiological Profile and Overall Survival in Patients with Pancreas Adenocarcinoma at a Referral Hospital in Oncology.** Brazilian Journal of Cancerology.DOI : 10.32635/2176-9745.RBC.2021v67n1.967. 2021.

[19]. Satoh et al. **Early Diagnosis to Improve the Poor Prognosis of Pancreatic Cancer.** Cancers.DOI : 10.3390/cancers10020048 . 2018

[20]. Liu et al. **Serum levels of IL-6, IL-8, and IL-10 are indicators of prognosis in pancreatic cancer** . Journal of international medical research. DOI: 10.1177/0300060518800588. 2018

[21]. Sakamoto et al **. Characterization of spatial distribution of tumor-infiltrating CD8+ T cells refines their prognostic utility for pancreatic cancer survival** . Nature. DOI: 10.1038/s41379-019-0291-z . 2019

[22]. Zhao et al **. Advances in the epidemiology of pancreatic cancer: Trends, risk factors, screening, and prognosis** . Cancer Letters. DOI: https://doi.org/10.1016/j.canlet.2021.06.027. 2021 _

[23]. Wu G, Maharjan S, Kim D, Kim JN, Park BK, Koh H, Moon K, Lee Y, Kwon HJ. **A Novel Monoclonal Antibody Targets Mucin1 and Attenuates Growth in Pancreatic Cancer Model** . *International Journal of Molecular Sciences* . 19(7):2004. DOI: https://doi.org/10.3390/ijms19072004. 2018 _

[24]. Guo, Y., Zhu, H., Weng, M. et al. **Chemo preventive effect of Betulinicacid via mTOR - Caspases/Bcl2/ Baxapoptoticsignaling in pancreatic cancer** . BMCComplementMedTher 20, 178.DOI: https://doi.org/10.1186/s12906-020-02976-7. 2020 _

[25]. Seufferlein , Thomas, and Thomas J Ettrich . **Treatment of pancreatic cancer-neo adjuvant treatment in resectablepancreatic cancer (PDAC**). *Translational gastroenterology and hepatology* vol. 421, doi:10.21037/tgh.2019.03.05. 27 Mar. 2019

[26]. Saneja , Ankit. **Gemcitabine and betulinicacidco -encapsulated PLGA−PEG polymer nanoparticles for improved efficacy of cancer chemotherapy** . Materials Science and Engineering: C..DOI: https://doi.org/10.1016/j.msec.2019.01.026. 2019 _

[27]. Zhu, H., Wei, M., Xu, J. *et al.* **PARP inhibitors in pancreatic cancer: molecular mechanisms and clinical applications.** ***Mol Cancer*** 19, 49 2020.DOI: https://doi.org/10.1186/s12943-020-01167-9 , 2020.

[28]. Ferreira, A., Carolina *et al.* **86/90Y-Labeled Monoclonal Antibody Targeting Tissue Factor for Pancreatic Cancer Theranostics**. *Molecular Pharmaceutics 17* (5), 1697-1705 DOI: 10.1021/acs.molpharmaceut.0c00127. 2020

[29]. Amanam I, Chung V. **Targeted Therapies for Pancreatic Cancer.** ***Cancers*** **;** 10(2):36. DOI: https://doi.org/10.3390/cancers10020036 . 2018

[30]. Boldrini , L., Cusumano, D., Cellini, F. *et al.* **Online adaptive emmagneticresonance guided radiotherapy for pancreatic cancer: state of the art , pearlsandpitfalls**. *RadiatOncol* **14,** 71. https://doi.org/10.1186/s13014-019-1275-3. 2019 _

[31]. Barbara J. Kenner. **Early Detection of Pancreatic Cancer** . 2018. Pancreas. DOI: 10.1097/MPA.00000000000001024.

[32]. Thakkar et al **. Depression Preceding and Following a Diagnosis of Pancreatic Cancer: Results From a National, Population -BasedStudy**. Journalofneuroendocrinetumorsandpancreaticdiseasesandsciences.DOI: 10.1097/MPA.0000000000001635/. 2020

Camila Senna. "Pancreas Cancer: A Literary Review."*IOSR Journal of Pharmacy (IOSRPHR),* 12(7), 2022, pp. 01-11.