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A REVIEW ON PANCREATIC CANCER: ETIOLOLY, RISK FACTORS, DIAGNOSTIC INVESTIGATIONS

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ABSTRACT:

Pancreatic cancer is one with high mortality cancer in the world. Ninety percent of pancreatic cancer. Various factors is associated with an increased risk of pancreatic cancer including age, sex, race, genetic, history of chronic pancreatitis, diabetes mellitus, gallstone, obesity, Helicobacter pylori infection, smoking, diet, and pollution exposure. Unfortunately, 80-85% of patients present with advanced unresectable disease. Furthermore, pancreatic cancer responds poorly to most chemotherapeutic agents. Hence, we need to understand the biological mechanisms that contribute to development and progression of pancreatic tumours. Although screening for pancreatic cancer is currently not recommended for the general population, emerging evidence indicates that pancreatic surveillance can improve outcomes for individuals in certain high-risk groups. Overall, considerable progress is required to reduce the burden associated with pancreatic cancer. Recent, renewed efforts to fund large consortia and research into pancreatic adenocarcinoma are welcomed, but further streams will be necessary to facilitate the momentum needed to bring breakthroughs seen for other cancer sites.

KEYWORDS: Types, Etiology, Risk Factors, Diagnostic Investigations.

INTRODUCTION:

At number fourteen on the global cancer incidence list, pancreatic cancer (PC) is one of the top causes of mortality . PC patients have shown encouraging clinical responses as a result of the development of both traditional and cutting-edge treatment plans, including as immunotherapy, radiation, and chemotherapy. Although radiation and chemotherapy have shown to be effective in destroying cancer cells in order to increase patient survival, unintended side effects would unavoidably arise because of harm to healthy cells that is not supposed to happen . Due to its poor survival rate, prostate cancer (PC) ranks fourth in terms of cancer deaths but tenth in terms of incidence . .In 2020, 495,773 new PC cases and 466,003 fatalities occurred worldwide .

The two main malignancies of the digestive glands are pancreatic and liver cancers . Patients with pancreatic and liver cancer still have little chance of a full recovery except surgical resection. Most patients' distant or delayed metastases prevent them from receiving surgery . Pancreatic cystic lesions (PCLs) include a wide range of conditions, including neoplasms and adenocarcinomas, as well as non-neoplastic entities such cysts connected to inflammation . About 80% of these lesions are non-neoplastic PCLs, which are frequently linked to pancreatitis . Ethically, there are differences in the distribution of pancreatic cystic neoplasm (PCNS).

Microbes are becoming increasingly significant owing to host-microbiome interactions that regulate various cellular physiological activities, such as immunity, inflammation, and cancer progression. Accumulating evidence suggests that microbiota and their products can alter the microenvironment of pancreatic tumors, impact the functionality of the immune system, and regulate the biological behavior of pancreatic cancer cells, thus promoting (or inhibiting) the progression of pancreatic tumors ..

The lack of usual early symptoms and the cancer's quick spread to distant organs and the lymphatic system may be the causes of pancreatic cancer's high death rate. As a result, when the diagnosis is made, 80% of patients already have metastases or an advanced local stage. As a result, treating this ailment with curative therapy is harder. A recurrence occurs in 80% of patients within the first two years following curative surgery..

EPIDEMIOLOGY:

Most of the Western world is seeing an increase in pancreatic cancer cases. Although pancreatic cancer is not as common as many other major cancer groups overall, its high lethality rate and rising prevalence in the aging population are making it one of the leading causes of cancer-related fatalities very quickly.

ETIOLOGY:

According to histology, exocrine or endocrine pancreatic tissue can give rise to pancreatic cancer. The exocrine tissue of pancreatic ductal adenocarcinoma is where the bulk (90%) of pancreatic cancer starts . A pancreatic cancer often affects the head of the organ, the body, and the tail of the organ in around 70% of cases . Exocrine pancreatic cancer tissue is referred to as pancreatic cancer in this article's terminology. There is still much to learn about the primary cause of pancreatic cancer, although a number of factors—a combination of endogenous and external factors—may raise the risk of developing the disease. Exogenous risk factors include nutrition, pollution exposure, smoking, and chronic pancreatitis illness history. Endogenous risk factors include genetics, age, sex, race, and history of gallstones, obesity, diabetes mellitus, stomach infection by Helicobacter pylori (H. pylori), along with diabetes.

PATHOPHYSIOLOGY:

The traditional pre-neoplastic lesions known as pancreatic intraepithelial neoplasia (PanIN) are the most common cause of pancreatic cancer, but bigger precursor lesions such as intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms can also cause the disease . The proliferation, migration, invasion, and metastasis of pancreatic cancer cells are facilitated by abnormal autocrine and paracrine signaling cascades that are displayed by the disease. .. For instance, a variety of signaling molecules, including hepatocyte growth factor (HGF), insulin-like growth factor 1 (IGF1), fibroblast growth factors (FGFs), and transforming growth factor-α (TGFα), as well as the tyrosine kinase receptors that bind to them, including EGFR, receptor tyrosine-protein kinase erbB-2 (ERBB2; also known as HER2), HER3, IGF1 receptor (IGF1R), FGF receptors (FGFRs), and HGF receptor (HGFR; also known as MET), enhance multiple pathways that support migration and invasion in pancreatic cancer cell. Nuclear factor-κB (NF-κB), AKT , and signal transducer and activator of transcription 3 (STAT3) are examples of pro-survival and anti-apoptotic pathways that are active in tandem with these signaling cascades. In certain cases of pancreatic cancer, genes including WNT, SHH, and NOTCH that are typically active throughout development are also reactivated .

TYPES OF PANCREATIC CANCER:

Acute pancreatitis (AP) and chronic pancreatitis (CP) are the two forms of pancreatic inflammation. Despite the fact that AP and CP are both benign disorders, PC is connected to them in various ways. CP, in contrast to AP, is a chronic inflammatory pancreatic illness characterized by exocrine gland insufficiency and calcification . Since pancreatitis and PC can coexist and lead to cancer, there is mounting evidence that lncRNAs are important in the development of pancreatitis-related PC.

A. ACUTE PANCREATITIS:

Gallstones and alcohol misuse are the usual causes of AP's localized and systemic inflammation. Most patients have minor AP when they first arrive, and this often goes away in a week. Pancreas or peripancreas necrosis or organ failure occur in only 20% of people with mild to severe AP. Recent studies have shown that there is a significant relationship between AP and PC and that lncRNAs have a non-negligible impact on this relationship. According to Kirkegard J et al.'s nationally matched cohort study of Danish adults, AP patients had higher absolute 2- and 5-year risks of PC among patients with AP of 0.70% (95% CI 0.62–0.78%) and 0.87% (95% CI 0.78–0.97%), respectively, during the first two years of follow-up compared to controls (adjusted HR 19.28; 95% CI 14.62–25.41)[26] Meanwhile, a crucial component of AP that encourages inflammation and cell death in diseased glandular follicles is elevated intracellular Ca 2+.

B. CHRONIC PANCREATITIS:

Pancreatic fibrosis, islet cell loss, and inflammation of the pancreas occur in chronic pancreatitis (CP). Regular episodes of CP can lead to exocrine and/or endocrine insufficiency, which can result in abnormalities of the pancreatic enzymes. Furthermore, CP can induce cellular DNA damage, modify chromosomes, and activate oncogenes via harming pancreatic cells' endoplasmic reticulum, mitochondria, and lysosomes. Through a meta-analysis conducted in 2017, Kirkegard J et al. found that within two years of diagnosis, people with CP had a 16-fold higher chance of developing PC than those without the illness. Pancreatic fibrosis is a common pathology feature of all CP types, and the activation of pancreatic stellate cells (PSCs) is a major contributor to this pathology. New research elucidates the function of long noncoding RNAs (lncRNAs) in liver, heart, and lung fibrosis.

It has been demonstrated by numerous previous research that individuals with CP are much more likely to develop PC, particularly in the initial years following diagnosis. PSCs control the synthesis of extracellular matrix while being dormant in normal circumstances. But cancer and CP can also activate PSCs, which in turn provides an environment that is favorable for the growth of PCs. PCs are further encouraged by PSC activation through four mechanisms: (1) hyperfibrosis; (2) tumor metastasis; (3) induction of resistance to chemotherapy and radiation; and (4) stimulation of the immune system . PSC activation has emerged as a focal point for PC and CP-associated fibrosis research. When cocultured with PC cells, PSCs significantly increase the growth and metastasis of cancer cells and produce a pro-tumor paracrine effect that lessens gemcitabine-induced pancreatic cancer cell apoptosis.

RISK FACTORS:

Risk factors for PC can be categorized as either modifiable (intestinal microbiota, smoking, alcohol, chronic pancreatitis [CP], obesity, dietary variables, infection) or non-modifiable (age, sex, location, blood group, family history and genetic vulnerability, diabetes).

1. NON MODIFIABLE RISK FACTORS:

A. AGE:

It is highly rare for young people under 30 to develop PC, and the disease often affects older folks.Ninety percent of newly diagnosed individuals are older than fifty-five, with the majority being in their seventies or eighties.

B. SEX:

Globally, women experience a lower incidence of PC than men do. In industrialized nations, this disparity is much more noticeable. It might be as a result of women's higher steroid levels than men's, which may offer protection against PC. By using a matched cohort study were able to confirm that women who had menopausal hormone therapy (MHT) had a 23% lower incidence of pancreatic cancer than women who did not receive MHT.

C. AREA:

Around the world, there are regional variations in PC incidence. Asian Americans and people from Pacific Islands have the lowest frequency in the United States, while African Americans have a greater incidence than Caucasians. The incidence of cancer is rising in China, and its growth rate in recent years has been consistent with global trends. Urban morbidity and mortalit y are higher than those in rural settings, possibly as a result of disparities in the socioeconomic environment and lifestyle.

D. BLOOD GROUP:

The whole surface of red blood cells is covered in the ABO blood group antigen. Blood type antigens influence the risk of PC, according to recent studies]. Individuals with diabetes who belong to the type A, AB, or B blood groups are more likely to acquire PC than type O patients .According to certain data, diabetes and the type A blood group will both contribute to the development of PC .The mechanism may be related to the promotion of cancer growth and metastasis and involves the modulation of the host inflammatory process associated with the ABO blood group. The ABO antigen-encoding gene has been linked to a number of plasma components, including tumor necrosis factor (TNF) and soluble intercellular adhesion molecule-1 (sICAM-1)].

E. GENETIC FACTORS:

According to recent research, PC is clearly inherited, and having a family history of the condition significantly raises the likelihood of developing the illness .Specific genetic mutations account for a limited percentage of PC cases, with over 80% of cases being caused by random mutations. PC is mostly caused by hereditary and acquired gene mutations. An exponential rise in the number of first-degree relatives is associated with an increased risk of familial PC .

F. DIABETES:

People with diabetes have a markedly higher risk of acquiring PC, according to modern epidemiology .Patients with type 1 diabetes who have had the condition for longer than ten years have a five-to ten-fold increased risk of PC. Individuals with diabetes who have had the condition for longer than 20 years are more likely to develop PC. A recent study that followed up on 7.5 million individuals found 2002 incidences of PC. Patients newly diagnosed with diabetes have an almost seven-fold greater risk of PC compared to those without the disease. One month prior to the diabetes diagnosis, the levels of blood glucose and glycated haemoglobin (HbA1c) in these PC patients increased considerably. As a result, HbA1c is anticipated to be a possible biomarker for PC .

2. MODIFIABLE RISK FACTORS:

A. HUMAN MICROFLORA:

A wide range of species, including bacteria, viruses, fungus, and protozoa, make up the human microbiota .Both human health and disease states depend heavily on them. Research indicates that there is a strong correlation

between the human microbiome and the incidence, progression, and prognosis of prostate cancer .Certain hepatitis viruses, bile, and oral, gastrointestinal, and pancreatic microorganisms may have possible etiological impacts in the development of PC . The following are the main ways that the microbiota contributes to the development of cancer.

B. IMMUNOMODULATORY ACTIVITY:

Numerous innate and adaptive immune responses that are involved in the development of tumors are triggered by the gut microbiota .By identifying flabellin, lipopolysaccharide (LPS), peptidoglycan, Toll-like receptor (TLR), and Nodlike receptor (NLR), the innate immune system controls the composition of microorganisms .. The pancreatic microbiota stimulates both innate and adaptive immune suppression, which in turn drives the development of pancreatic tumors ..

C. MICROBIAL METABOLITES:

Microbiolgical goods Short-chain fatty acids (SCFAs), lipoteichoic acid (LTA), and secondary bile acids all have significant effects on the proliferation of cancer cells.. LTA and secondary bile acids are two of them that encourage the development of malignant trans. LTA mostly attaches to particular differentiation clusters, which causes an overabundance of pro-inflammatory proteins to be secreted.By activating G-protein coupled receptor 1, secondary bile acids cause aberrant cell growth and damage to cellular DNA (GPBAR1).By supporting Treg-mediated immune control, SCFA can have the opposite anti-inflammatory and anti-cancer effects of LTA and secondary bile acids. PDAC is brought on by metabolites that enter the body through the intestines and interact with pancreatic cells. There is still no clear explanation of the precise process .

D. MICROBIOTA DYSBIOSIS:

There is less microbial diversity in the colon and other body organs when the human microbiome system is dysregulated. Its occurrence is linked to host gene alterations, which eventually have an impact on the body's normal immune system .There are several elements that can impact the body's normal microbial system, including but not limited to nutrition, sex, genetics, hormones, and bile acids .Recent research has demonstrated that the gut microbiota and intestinal immunity are shaped by mediators released by the pancreatic acinus. When scientists gave mice antibiotics continuously, they created microbial problems in the mice and discovered a markedly increased prevalence of PC and other extraintestinal cancers . An increasing amount of data points to a connection between microbial dysbiosis and PDAC susceptibility, incidence, and prognosis.

E. CONNECTIVITY BETWEEN VIRULENCE AND MICROBIAL TOXINS:

Certain bacterial toxins can lead to auto-immune diseases, cellular DNA destruction, and persistent inflammation . For instance, cytotoxins that harm host cell DNA, such as aflatoxin, mycotoxin, and collidin, are implicated in the development of cancer.

F. PANCREATIC INTRACELLULAR MICROBIOTA:

The pancreas secretes a significant amount of extremely alkaline pancreatic juice and proteases, which has long been thought to be the reason why most bacteria cannot thrive there . However, some researchers have found that the number of microorganisms in the pancreas of PDAC patients is 1000 times that of the normal control group by RNA probe and PCR technology . Patients with PDAC had significantly higher levels of Bifidobacteria, g-Proteus, H. pylori, and Clostridium bacteria in their pancreas, according to a comparative investigation. Proteus g may be connected to gemcitabine, an anticancer medication, and drug resistance . Clinical research has demonstrated that H. pylori activates pathways that regulate pancreatic PDAC growth and progression, which may be connected to PC's cancerous nature. When it comes to PC prognosis, having Fusobacterium might drastically reduce a patient's odds of survival.

G. ALCOHOL:

People who drank more than 30 g of alcohol per day had a considerably greater risk of disease (RR: 1.22, 95% confidence interval (CI): 1.03 1.45), according to a cohort analysis of 2187 PC patients . A meta-analysis also revealed a dose-response link between alcohol consumption and risk in high-drinking populations, but no association between low- and moderate-drinking alcohol and PC risk.

H. DIET:

A 30- to 50% higher chance of getting PC is directly linked to high consumption of fried food, nitrosamine-containing foods, grilled and processed meat, and high-cholesterol foods. A high diet of fruits and vegetables was linked to a lower chance of developing PC, according to a qualitative analysis of case-control studies . Red meat as a risk factor, however, has yielded conflicting results.

I. OBESITY AND PHYSICAL INACTIVITY:

As a risk factor for PC in both sexes, obesity and elevated BMI were found to be positively correlated in a previous meta-analysis study. A different meta-analysis research with 21 separate prospective trials found that the RR for BMI was 1.10 for women and 1.16 for men. In a study of racial disparities caused by smoking and obesity in Black males, the biggest correlation was seen between BMI and PC mortality .Obese individuals were shown to have a 20% increased risk of PC, and inactivity may further raise PC risk .

J. WORK PLACE EXPOSURE TO CERTAIN CHEMICALS:

According to the American Cancer Society,prolonged occupational exposure to specific chemicals used in the metalworking and dry cleaning sectors may raise the risk of PC.

STAGING:

The stage of PC at diagnosis determines the prognosis and course of treatment. As a result, proper staging is essential. The Union for International Cancer Control (UICC) serves as the primary basis for staging. Patients with PC can be classified as "resectable," "borderline resectable," and "unresectable" based on a more straightforward practical staging approach that was established during surgical investigation in the past. Preoperative staging is now becoming available as more advanced imaging techniques are developed. Patients with stage I and stage II tumors are among those believed to have curable cancers.For people with stage IV PC, chemotherapy is the sole available treatment, whereas local therapies like radiation are thought to be an alternative for those with stage III PC. The "borderline resectable" group comprises patients who do not have distant metastases but have blood vessel involvement (>180∘ of the superior mesenteric artery, blockage, or deformity of a short segment). This consensus has been achieved in recent years. Neoadjuvant treatment may improve the prognosis for borderline patients.

SYMPTOMS:

Pain in the epigastrium is experienced by 70–80% of pancreatic cancer patients. The pain originates in the stomach region and might occasionally spread to the back and sides. The pain is reduced by leaning forward or staying motionless. Cholestasis symptoms, jaundice, an appetite loss that cannot be explained, depression, and occasionally diarrhea or steatorrhea are observed. Because the bile duct is obstructed by pancreatic tumors, a dark, increasing jaundice is observed. When a patient has indigestion, swelling, weight loss, lack of appetite, and chronic, persistent pain around the belly, navel, or stomach, the doctor should take pancreas cancer into consideration. If the tumor narrows the bile channels, the gallbladder will be palpable as vesicle hydrops (Courvoisier-Terrier findings).

SCREENING GROUPS:

Patients with certain conditions, such as Lynch syndrome, familial adenomatous polyposis (FAP), hereditary breast and ovarian cancer-BRCA1 and BRCA2 mutations, Peutz-Jeghers disease, familial atypical mole melanoma, cystic fibrosis of the pancreas, and familial cancer syndrommes, are at an increased risk of developing pancreatic cancer and should be screened for the disease using particular techniques.

SCREENING AND EARLY DETECTION:

Currently, there is no trustworthy screening tool available to screen the general public and identify pancreatic cancer in its early stages . Over the past ten years, there has been a notable rise in research on pancreatic cancer screening. A number of screening tests, such as the blood markers for pancreatic cancer CA19-9, SPAN-1, CA-50, DUPAN-2, cell surface associated mucins (MUC), carcinoembryonic antigen, and heat shock proteins, have been studied to help identify or diagnose pancreatic cancer earlier in the general population. But these tests have not been well studied yet . Researchers are working to develop effective screening tests that may be used to identify individuals who have an increased risk of developing pancreatic cancer, such as those with a family history of the disease, gene abnormalities in BRCA2, p16, HNPCC, familial pancreatitis, Peutz-Jeghers syndrome, and other histories. Currently, there are no screening tests available to screen the general population. Furthermore, it is unclear which entry points—stool, pancreatic juice, saliva, and blood—might be suitable for researching these prospective screening markers. While not thoroughly studied, some screening methods, such as spiral computed tomography and endoscopic ultrasound, show promise for individuals with a high risk of developing pancreatic cancer, including those with hereditary pancreatitis or those who have family members who have the disease. Screening can start at age 40 for patients with hereditary pancreatitis (in carriers of the PRSS1 mutation), who have an increased risk of early onset pancreatic cancer. About the appropriate time to start screening for people, there is no agreement. It's still a very interesting field.

INVESTIGATIONS FOR DIAGNOSIS:

- HISTOPATHOLOGICAL ANALYSIS:

For the diagnosis of PC, cytology and/or histopathology analysis represent the "gold standard." All other patients should aim with the exception of those receiving surgical resection. The microbiological system linked to pancreatic cancer. 4 Technology in Cancer Research & Treatment to establish a definitive pathology diagnosis prior to designing a therapeutic strategy. Currently available techniques for collecting specimens for histopathology or cytology include: (1) Computed tomography (CT) guided biopsy or endoscopic ultrasonography (EUS): (2) Ascites Cytology; or (3) Laparoscopic or Open Surgery Diagnostic Exploratory Biopsy.

- ENDOSCOPY ULTRASCOPY :

Endoscopy Ultrasonography is better than MDCT in the diagnosis of PC, according to a number of findings in the literature. The sensitivity of EUS and MDCT for PC diagnosis was 98% and 86%, respectively, in a retrospective study. Two widely used techniques in clinical investigations are endoscopic retrograde cholangiography-guided tissue specimens (ERCP-TS) and EUS-guided tissue specimens (EUS-TS). EUS-TS outperformed ERCP-TS in a prospective study including 125 patients when evaluating biliary strictures brought on by pancreatic illness, particularly PC.

- MAGNETIC RESONANCE IMAGING :

Thanks to advancements in magnetic resonance imaging (MRI) technology, there has been a lot of focus on PC surgical resectability, proper staging, and MRI results in recent years. Additionally, MRI can efficiently combine function and morphology by dynamically reflecting the mobility and chemical change of water molecules

within the lesion . The frequency of pathological staging and MRI staging did not differ significantly (P > 0.05). This finding suggests that the surgical staging and the MRI staging are entirely compatible. MRI results for PC staging I/II or III/IV revealed a sensitivity of 1.00 and a specificity of 0.67 . Two investigations have demonstrated that the specific MRI technique known as differential diffusion-weighted imaging (DWI) is crucial in differentiating between PC and mass development as pancreatic lesions can be accurately depicted with MRIDWI without exposing the user to radiation. When evaluating the resectability and preoperative staging of PC, MRI-DWI may have greater clinical significance than MDCT.

- CHEMOTHERAPY:

Chemotherapy plays a significant role in the all-encompassing PC treatment plan. Research has demonstrated that adjuvant chemotherapy following radical resection can markedly increase PC patients' overall survival as well as their disease-free survival. Modified leucovorin, 5-fluorouracil, irinotecan, and oxaliplatin (MFOLFIRINOX) is frequently used for gemcitabine and capecitabine for six months or for six months of adjuvant chemotherapy following radical resection. The FOLFIRINOX regimen, which combines chemotherapy with gemcitabine and NAB paclitaxel, is the recommended course of treatment for patients with metastatic PC. Gemcitabine is the first line of treatment if the patient is not a good candidate for combination chemotherapy. Gemcitabine (with or without erlotinib) paired with 54 Gy is the main choice for combination therapy with chemotherapy and radiation therapy for patients with locally advanced PC. At the moment, researchers.

- RADIOTHERAPY:

X-rays are used in radiation therapy to kill or harm cancer cells, preventing them from spreading. Patients with locally advanced PC are the primary candidates for radiotherapy. Numerous investigations have demonstrated that receiving chemotherapy was not superior to continuing chemotherapy in patients with advanced prostate cancer, nor did it increase patient survival . In clinical use, there are 4 main forms of radiotherapy: 1. External beam radiation therapy, which uses external radiation therapy sources that emit X-rays, gamma rays, electrons or heavy particles. However, the surrounding tissue is greatly damaged, and this treatment requires multiple courses of treatment; 2. Brachytherapy, which is mainly used for internal radiotherapy by surgery or laparoscopy in the pancreas or adjacent to the pancreas. It can be administered in the form of single or multiple scores and in combination with external radiation therapy.

- TARGETED THERAPY:

Patients with biomarker-specific gene mutations or other changes may benefit from targeted therapy as a first-line treatment option or as a follow-up treatment . For patients with solid tumors with neurotrophic tyrosine receptor kinase (NTRK) gene fusions, the FDA has approved larotrectinib and entrectinib, two oral tyrosine kinase inhibitors (TKIs) . Based on po oled analysis of singlearm basket studies involving a variety of solid tumor types in patients with verified NTRK mutations, these two TKIs were approved more quickly. Yet, NTRK mutations are incredibly uncommon; a meta-analysis of NTRK gene fusions found that their occurrence in PDAC patients was 0.31% (95% CI, 0.09 0.53). Furthermore, due to the extremely small number of NTRK-positive PDAC patients recruited, clinical trials involving larotrectinib and entrectinib have demonstrated low effectiveness readout specifically for PDAC . For the great majority of patients, NTRK targeted therapy is not an option; it is only for individuals with recurrent illness or metastatic PDAC who have poor performance status.

- IMMUNOTHERAPY:

Immune checkpoint blockade (ICB) therapy is currently licensed for treating a number of cancers, including head and neck squamous cell carcinoma, lung cancer, melanoma, and renal cell carcinoma. Nonetheless,

PC is thought to be a less immunogenic malignancy. It is believed that the microenvironment of PC tumors produces an environment that is immunosuppressive. As a result, immunotherapy has not yet been approved for PC patients. In PC, monotherapy of CTLA-4 or PD1 inhibitors is virtually useless. Several therapeutic trials have examined immunotherapy in conjunction with cytokine antagonists, chemotherapy, radiation, and vaccinations. Clinical research has revealed that the patient's immunological state remains unchanged despite the theoretical expectation that clinically relevant medication treatment would lower the immune response. Tumor macrophages exposed to radiation therapy may develop an immunosuppressive phenotype and lose their ability to mount T cell-mediated defenses against tumors, which will impede cellular immunity. That being said, the FDA has approved pembrolizumab for the treatment of microsatellite instability tumors regardless of the kind of cancer, defying the notion that radiation therapy impairs cellular immune function. This landmark investigation is still ongoing . Nevertheless, some cancers become resistant to ICB treatment and recur. The patient's reaction to ICB may be influenced by some intrinsic features of immunological and tumor cells, such as T cell infiltration; Innate immune cells and T cells stimulate MHC-1 molecule antigen presentation and differentiation . The results of a recent immunotherapy breakthrough study conducted in the United States revealed that interferon (IFNs) had a dual effect on the tumor immune response. Initially, IFNs stimulate dendritic cells to facilitate the cross-activation of tumor-specific CD8þ T cells. However, prolonged exposure to IFNs might result in negative feedback, which prevents T cells from producing immunosuppression. There has been progress in another study on increasing the effectiveness of tumor immunotherapy. Research has demonstrated that blocking the IFNG signaling pathway in tumor cells can boost the body's resistance to innate immune destruction or malignant cells, as well as increase the effectiveness of immunotherapy.

- MICROBIAL THERAPY:

The human microbiome is now strongly shown to be important in controlling the course of cancer and how the disease responds to therapy. It influences how parenteral and intestinal tissues react to cancer treatment . In one investigation, the researchers used intestinal bacterial extracts from PC hosts to transplant into a mouse model. They discovered that the patient's bacterial extract contained macrophages, which inhibited the activation of CD4þ and CD8þ T cells. Different pattern recognition receptors (PRRs) in tumor macrophages are more activated when they are unable to present antigenic macrophage antigens. PCs that develop in hosts that have had their antibiotics removed, however, have drastically different outcomes. Though the mechanism is yet unknown, intestinal microflora has been shown to create tumor-specific immunity as well as systemic immunity in PC patients. For instance, it's not apparent if gut bacteria must influence local antigen presentation in tumors and tumor draining lymph nodes, or if they can only control cancers that impact immune cells in distant intestinal/intestinal-associated lymphoid tissue barriers. Differential effects of metabolites generated from microbes have also been documented to control PDAC immunity. Probiotics and clinically focused synthetic microorganisms with a tumor target are challenged by this. However, it is still unknown how microbial-matrix interactions and metabolites produced by microbes play a part in metastatic illness . Numerous investigations have demonstrated the significance of gut bacteria and human microorganisms in the PC tumor microenvironment, and fecal transplantation, a kind of microbial conditioning, is a promising possibility for upcoming clinical trials. In the future, studies will concentrate on the role that microflora plays in the development and maintenance of immunological tolerance in an effort to identify new therapeutic approaches. Through a thorough examination of the microflora associated with PC, certain communities that contribute positively or negatively to the onset and spread of PC can be identified, opening the door to more targeted approaches for response modulation.

CONCLUSION:

This review provides a comprehensive account of the epidemiology and management of pancreatic cancer (as highlighted in the summary section above) remain in the understanding of this disease and treatment options although continually evolving continue to have limited success. There has been a recent drive to fund large consortia and specialist research into pancreatic cancer but there is much work to be done to enable similar breakthroughs as seen for other Cancer sites.

Pancreatic cancer is one of the deadly cancers in the world. It is often diagnosed lately at advanced stage due to no typical early symptoms of the cancer. Moreover, no screening test having a good sensitivity to detect the cancer at early stage is available until now. Further studies to find a more sensitive and specific diagnostic tool as well as the more effective treatment modalities for pancreatic cancer are necessary.

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