INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

"The Silent Killer": A Comprehensive Review of Pancreatic Neuroendocrine Tumor

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ARTICLE INFO

Published: 22 Nov 2025
Keywords:
Pancreatic neuroendocrine tumor (PNETs), Aggressive cancer, Silent Killer, Advanced
DOI:
10.5281/zenodo.17678335

ABSTRACT

Pancreatic neuroendocrine tumor is highly aggressive and often goes undetected until it has reached an advanced stage because early symptoms are rare and there are no reliable screening methods. It has high rates of incidence and death, especially among men and older adults, making it a major global health concern. Most cases are pancreatic ductal adenocarcinoma, which has a five-year survival rate below 10% and a poor outlook. Risk factors include smoking, alcohol use, obesity, type 2 diabetes, acute and chronic pancreatitis, genetic factors, and metabolic syndrome. Treatments such as surgery, chemotherapy, and radiation are available, but outcomes remain unsatisfactory. Diagnosis is challenging and relies on imaging and biomarkers. Current research aims to improve early detection, prevention, and treatment by studying molecular mechanisms, risk factors, and multidisciplinary care. So, the pancreatic neuroendocrine tumors are referred to as the silent killer disease since the initial signs are somewhat infrequent but very vague hence only postpones the diagnosis. In this review, a complete pharmacology of pancreatic cancer is covered.

INTRODUCTION

Something I was reading about were the pancreatic neuroendocrine tumor and frankly speaking, they are frightening cancers not only to the patients but also to the doctors themselves. These tumors may locally extend and cause complications, thus their survival is rather low, and it is not easy to detect and treat them in their initial stages. In my most recent research, I found that pancreatic neuroendocrine tumors rank third in the US and seventh worldwide in terms of cancer-related mortality, based on GLOBACON data from 2018.[1]

Clinically, PNETs patients only exhibit symptoms at an advanced stage when they visit a medical centre.[2] Early lesions are clinically asymptomatic but have a favourable prognosis. Since there are currently no accurate and efficient screening

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

methods or tests, early-stage PNETs diagnosis is uncommon.[3] If therapy is planned to cure PNETs patients, surgery is the cornerstone of treatment.[4]

Pancreatic neuroendocrine tumors (PNETs) resemble one of the most aggressive solid tumors with regard to aggressiveness. We usually only notice them after they are already quite developed and as a rule the first treatment option is to administer chemo, but there are occasions when they respond quite successfully to a specific set of therapeutic techniques. [5] One of the deadliest cancers, pancreatic neuroendocrine tumor (PC), is an aggressive illness. Although these are the rarest type of malignancy, PNETs provide the fourth most common source of malignant demise in the world and the third in the United States alone.[6]

The reason could be the high mortality rate of pancreatic neuroendocrine tumor which propagates ultra-fast to distant organs and lymph nodes and which none of the signs are evident early. Consequently, 80% of patients already have metastases or a locally advanced state at the time of diagnosis.[7] With an anticipated 367,000 new cases identified worldwide in 2015 and an accompanying 359,000 deaths, this tumor offers a serious health risk.[8]

Most individuals do not show any obvious symptoms when the disease advances to advanced pancreatic metastases, when the tumor cells are very invasive. It is currently among the deadliest malignant tumors, and early identification is difficult.[9] Hence, approximately, the second source of cancer related death in the U.S. by the year 2030 is pancreatic neuroendocrine tumors (PNETs).[10] About 90% of cases of pancreatic neuroendocrine tumor are adenocarcinomas. Additional subtypes include acinar carcinoma, neuroendocrine tumor, and pancreatic blastoma.[11]

1.1 WHAT IS PANCREASE?

One of the organs in the belly, the pancreas, releases fluids that aid in the body's breakdown of meals. Additionally, it produces hormones that help regulate blood sugar levels.

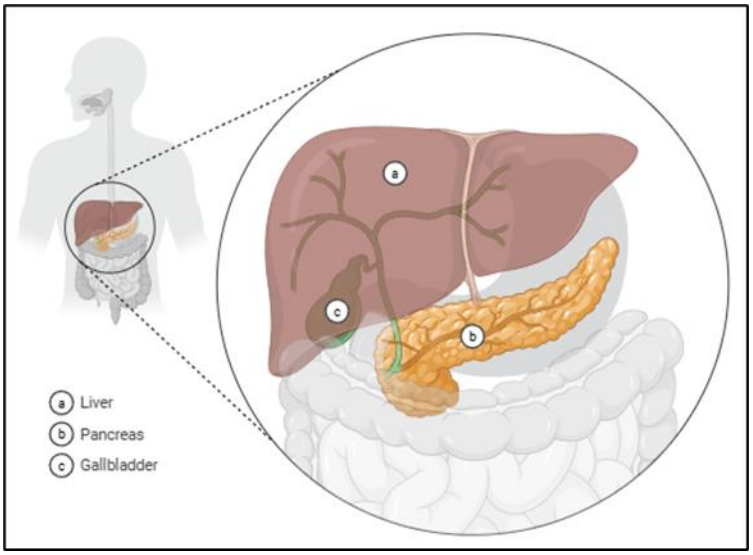

FIGURE 1: Diagram showing the location and anatomical representation of the pancreas

1.2 WHAT IS MEAN BY PANCREATIC NEUROENDOCRINE TUMOR?

Pancreatic neuroendocrine tumor is a condition characterized by atypical cellular proliferation and development. This illness typically spreads

quickly to surrounding organs and is difficult to detect early since symptoms do not appear immediately. When symptoms do appear, they are frequently ambiguous and may go ignored.[12] There is no efficient screening. In contrast to 5.26% in 2000, the 5-year survival rate finally surpassed 10% in 2020.[13]

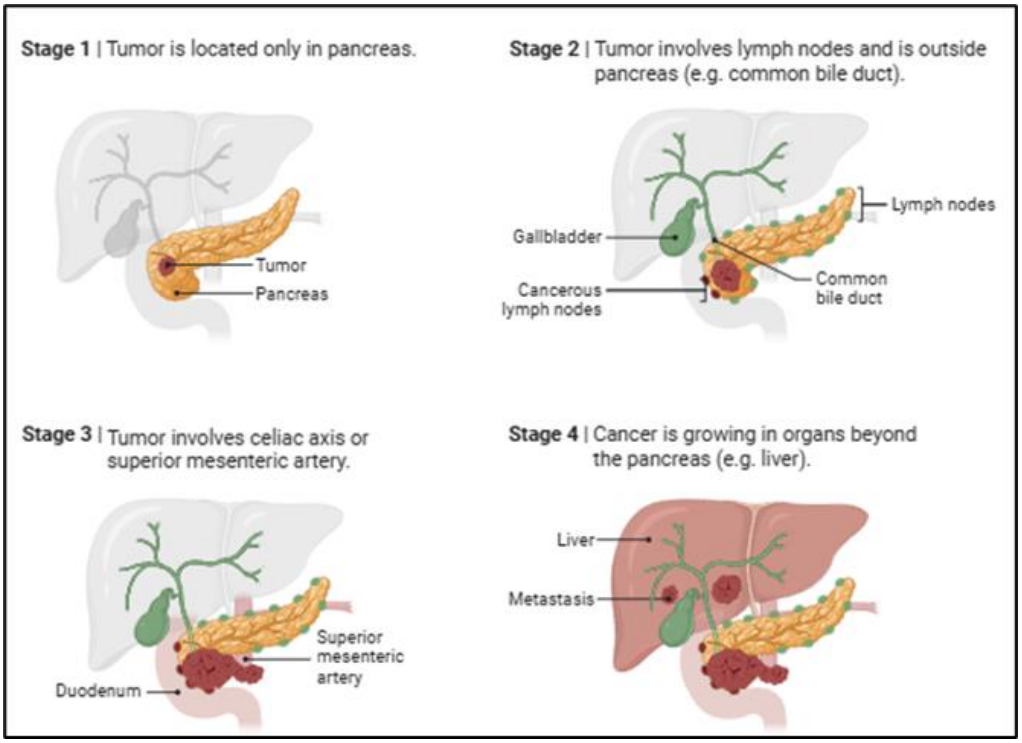

FIGURE 2: Diagram showing pancreatic neuroendocrine tumor and the stages involved in developing pancreatic neuroendocrine tumor

1. EPIDEMOLOGY

Analysing the epidemiology of pancreatic neuroendocrine tumor may be essential to understanding its aetiology and, thus, the basis for creating a successful preventative plan. Pancreatic neuroendocrine tumor is a global health concern due to the vast regional variations in its incidence and death rates. In 2018, there were about 458,918 new cases reported worldwide.[14] Europe and North America have the greatest incidence rates, with age-standardised rates (ASRs) as high as 11.2 per 100,000 reported in nations like Hungary. Conversely, Southeast Asia has some of the lowest incidence rates (around 1.6 per 100,000). These regional differences reflect differences in risk factor prevalence, healthcare accessibility, and diagnostic proficiency.[17]

2.1 INCIDENCE

Different demographics and geographical areas have different rates of pancreatic neuroendocrine tumor (Fig. 3). Thus 2018 according to the recent statistics had 458,920 newly diagnosed pancreatic neuroendocrine tumors in the world which is equivalent to 2.5 percent of all the cancer cases.

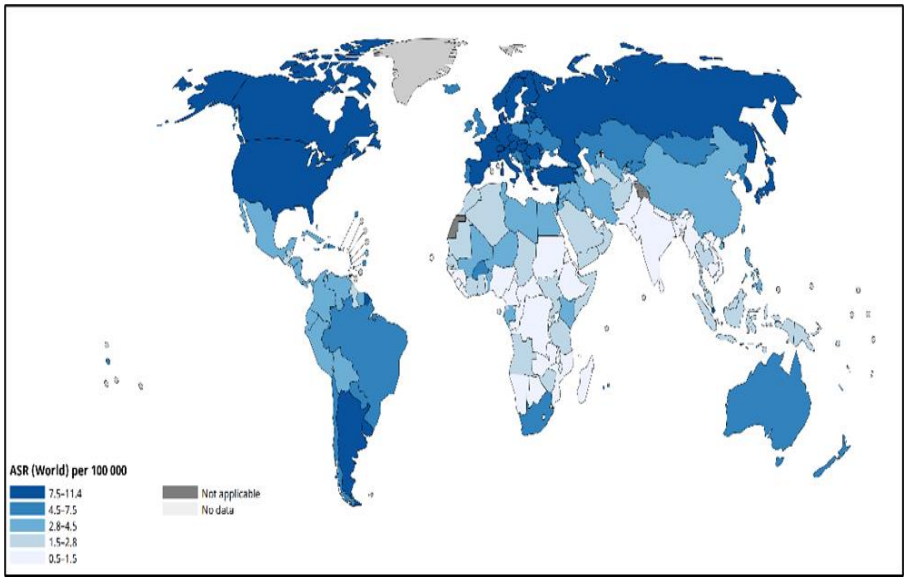

FIGURE 3: The map demonstrates the world age-adjusted incidences (ASR) of pancreatic neuroendocrine tumor in all ages and gender in 2018. (reproduced from Global Cancer Observatory).

Thus, Asia (232537/45.5) and Europe (146478/28.8) are ranked on the first positions in terms of ASR incidence and North America (67089/13.2) and Latin America and the Caribbean (41032/8%) are ranked in the after positions.With 918994/3.8% of the population, Africa had the lowest rate. Additionally, Oceania (4864/0.95%) (Fig. 4). [18]

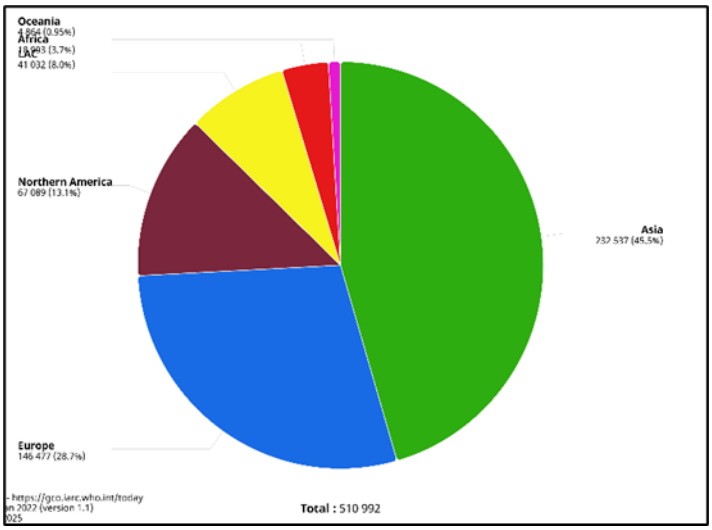

FIGURE 4: The map displays the anticipated global incidence and absolute numbers for pancreatic neuroendocrine tumor in both male and female sexes in 2022. (reproduced from Global Cancer Observatory).

TABLE 1: In essence, therefore, this tabular presentation is the projected global PNETs cases in 2022, both males and female.[19]

Label	Cancer Code	Country Code	ASR (World)	Crude Rate	Total
Africa	13	903	2.4	1.4	18 993

Latin America and the Caribbean	13	904	4.6	6.2	41 032
Northern America	13	905	8.5	18.0	67 089
Europe	13	908	80.	19.6	146 477
Oceania	13	909	6.2	11.1	4 864
Asia	13	935	3.6	5	232 537

The higher the age of a person, the higher the number of people to whom the pancreatic neuroendocrine tumors are found; hence, these diseases are virtually an elder disease, with the highest occurrence observed among those past 70 years of age. [21, 22]

2.2 MORTALITY

Pancreatic neuroendocrine tumor death rates vary widely across the globe (Fig. 5). Western Europe had the greatest death rates in 2018 (7.6 /100,000 persons), Based on the data, Central and East Europe (7.3), North Europe, and North America (both at 6.6) (Figure 5). [1] lagged behind. The lowest rates were observed in East Africa (1.4), South -East Asia and West Africa (both at 2.1). Nearly 90% of all pancreatic neuroendocrine tumor fatalities happen beyond the age of 55, and the mortality rate rises with age in both males and female sexes.[18] The highest rates of male mortality in 2018 were seen in Uruguay (12.1) and the Republic of Moldova (12.3), while the United Arab Emirates (10.0) and Uruguay (8.1) had the highest female mortality rates. In contrast, Tanzania (0.3) and Malawi (0.32) had the fewest fatalities among males, while Guinea (0.2) and Pakistan (0.3) had the lowest deaths among women.

The deadly character of pancreatic neuroendocrine tumor is shown in the striking similarity between the disease's incidence and death rates.[23, 24]

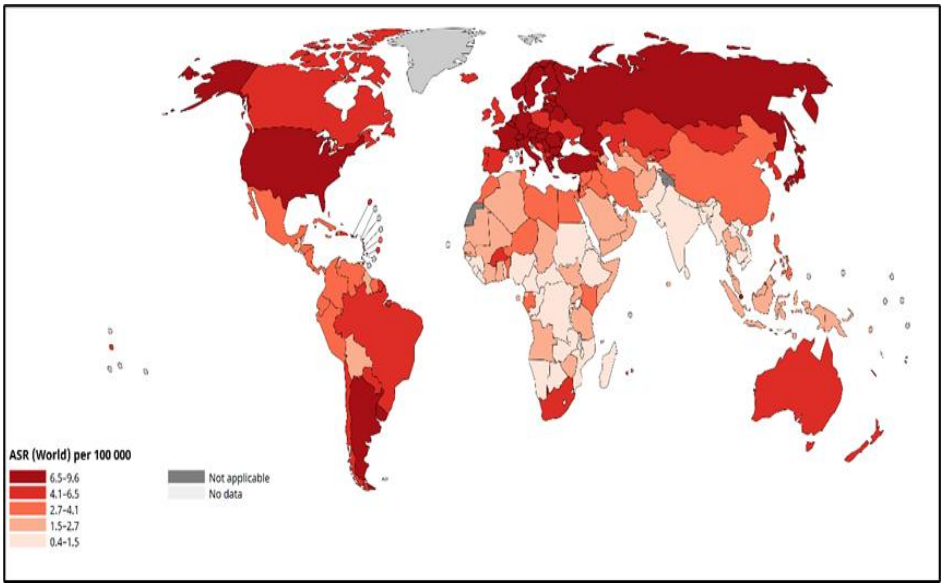

FIGURE 5: Thus, there is a map indicating age-standardized mortality rates of pancreatic neuroendocrine tumors among populations globally in 2018. It has all the age categories and indicates the rates of both men and women. (reproduced from Global Cancer Observatory).

2.3 SURVIVAL RATE

I have some data on the five-year survival on pancreatic neuroendocrine tumor, it actually improved by 6.1 to 9.2 percent between 2014 and 2018, It is some progress, sure, but frankly we are still running to increase those figures even more. Because of its poor prognosis and 94% mortality/incidence ratio, pancreatic neuroendocrine tumor is really still one of the deadliest illnesses.[18]

The US National Cancer Institute reports that, regardless of gender or ethnicity, 10% of patients with PNETs the rate of survival of the identified patients in the local stage was 32% in 2014-2018. I only read this stuthein which the EUROCARE-5 Working Group considered the facts of patients with pancreatic neuroendocrine tumors identified between 2000 and 2007 using the cancer registries data available in 29 European countries.

Women survival rate has in fact risen by 20 percent within the year as compared to the 11 percent. This is however No longer true since 1970s, the 5- and 10-years survival of pancreatic neuroendocrine tumors did not improve. (Table 2).[27]

TABLE 2: Survival Rates by Pancreatic neuroendocrine tumor Clinical Stage

Clinical Stages	Five-Year Survival %	
	Exocrine pancreatic Ductal Adenocarcinoma	PanNET Treated with Surgery
STAGE-1B	14 %	61 %
STAGE -IB	12 %	61 %
STAGE -2	07 %	52 %
STAGE -3	03 %	41 %
STAGE - 4	01 %	16 %

In one study (2011) conducted, a connection was observed between smoking and approximately a quarter of all pancreatic neuroendocrine tumor cases in men (26.2) and 1/3rd in women (31.0) in the United Kingdom..[29] In contrast, there are more smokers in China and India, the two most populated countries in the world, than there are in all of Europe.[30]

2. RISK FACTORS

Early diagnosis and the capacity to identify and screen high-risk groups before the onset of symptoms are critical for the detection of pancreatic neuroendocrine tumor (PNETs) when it may be cured. It is difficult to identify a high-risk group, and the best screening methods are yet unknown.[31]

Getting a PNETs is rather rare for young individuals under thirty, and it usually affects older people. Ninety percent of those who receive a new diagnosis are over fifty-five, and most of them are in their seventies or eighties.[9] Pancreatic neuroendocrine tumors are becoming more common in the majority of Western nations. Despite being less common than many other major cancer groups, pancreatic neuroendocrine tumors are rapidly becoming the most common reason of tumour-associated demise because of their elevated lethality rate and increasing prevalence in the elderly population. [12, 15]

PNETs risk factors are classified as either non-modifiable or modifiable.[9]

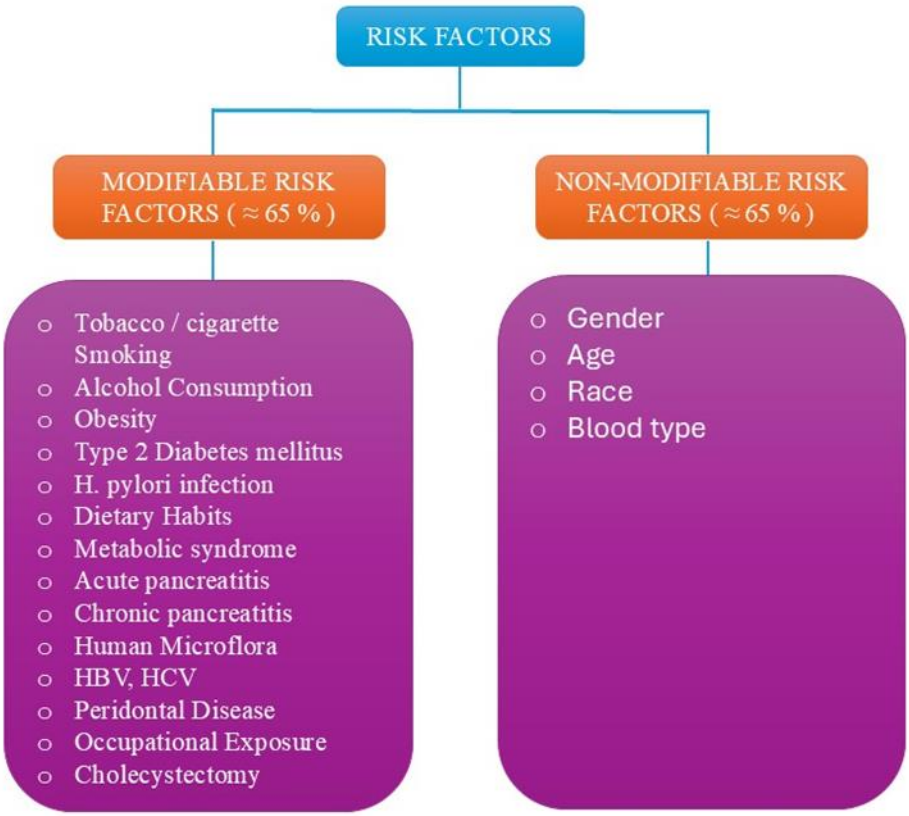

FIGURE 6: Risk factors that contribute to pancreatic neuroendocrine tumor development. [33]

3.1 MODIFIABLE RISK FACTORS FOR PNETs

a) Tobacco Smoking / Cigarette Smoking

People who smoked fewer than 30 cigarettes a day already had a greater risk of getting PNETs, A recent quantitative systematic reviewof Lugo et al. that included 78 observational studies observed that the risk of PNETs rises after some years of smoking and reaches a peak after approximately three decades [35] , and decreases rather fast with abstinence. A quantitative systematic review of 82 epidemiologic studies by Iodice et al. [36] showed an overall risk of 1.74 (95 numbers below 1.61 1.87) based on the current smokers and 1.2 (95 numbers below 1.11 1.29) based on the former smokers. Nitrosamines found in cigarettes cause pancreatic neuroendocrine tumors in animal models, and carcinogens enter the pancreas by blood bloodstream or refluxed bile.[37] The duration and intensity of cigarette smoking affect the risk of pancreatic neuroendocrine tumor, which is about doubled.[38]

b) Alcohol Consumption

A cohort analysis of 2187 PNETs patients found that those who drank more than 30 g daily had a considerable higher potentiality of illness (RR: 1.22, 95% confidence interval (CI): 1.03 1.45).[39] According to case-control research by Rosato et al. [42], excessive alcohol consumption was linked to 13. non-tumour smoking to 13.6%.[42]

c) Obesity

Lipid oxidation and biosynthesis are critical for the survival of rapidly growing cancer cells. Fat can increase the viability of cancer cells as compared to non-tumor tissue.[43] PNETs formation is stimulated by dysfunctional visceral and

subcutaneous adipose tissue via a complex molecular process. Proinflammatory cytokines and adipokines are released when adipose tissue experiences hypoxia and mild inflammation due to excessive fat buildup.[45]

d) Type 2 Diabetes Mellitus

As recent epidemiology statistics show, individuals with diabetes are far exposed to the risk of getting PNETs. [46]. PNETs occur in type 1 diabetics with a history of over ten years at least by a factor of five to ten. PNETs is more common among those who have had diabetes for more than 20 years.[47] A recent research that followed 7.5 million people found 2002 PNETs instances. Patients with newly diagnosed diabetes are around seven times more likely to have PNETs than people without the disease.[9]

In addition to raising the risk of developing pancreatic neuroendocrine tumor, long-term diabetes mellitus also contributes to the disease and is a consequence of early-stage pancreatic neuroendocrine tumor.[49] New-onset diabetes mellitus may be the first sign that an elderly patient has pancreatic neuroendocrine tumor since pancreatic neuroendocrine tumor (type 3c diabetes mellitus) can also cause diabetes mellitus.[49, 50]

e) Ulcerative stomach disease

Peptic ulcer illness and gastric cancer are known to be associated with Helicobacter pylori infection of the stomach mucosa, particularly with the cytotoxic strain (CagA+). Some studies claim that it may also aid in the advancement of PNETs. [51] The traits of the bacteria brought about by their virulence and the way the microbe interacts with the human immune system both influence this impact.[53]

It's interesting to note that proton pump inhibitors (PPIs), which are used to eradicate H. pylori, might result in hypergastrinemia, which may encourage the development and advancement of PNETs. Therefore, there are reasons to use caution when administering this class of medications to individuals who have a high risk of PNETs.[54] H pylori infection may raise the risk of pancreatic neuroendocrine tumor through several tenable molecular processes. Reduced absorption of antioxidants like vitamin C is one of the secondary effects of H pylori-induced gastritis.[55] and hypergastrinemia, which promotes the proliferation of pancreatic neuroendocrine tumor cells.[56, 57]

f) Dietary Habits

Foods are known to predispose people to various diseases, but it is challenging to establish a link between a particular dietary component and the chance of developing cancer. [33]

Red Meat

The relationship of meaty-risk is in line with experimental studies that have discovered high-temperature meat cooking, particularly the red meat, causes the formation of carcinogenic chemicals in sewer rats and human subjects. [58]. A quantitative systematic review of 11 cohort studies identified a favourable correlation among the risk of developing pancreatic neuroendocrine tumors and consuming a lot of red (>120 g/day) or processed (>50 g/day) meat.[59] A quantitative systematic review [60] of 28 relevant articles (case-control and cohort studies) was carried out in 2017 by Zhao et al. Red and processed meat ingestion was found to be strongly associated with the risk of PNETs in case-control studies, but the data from cohort studies showed no evidence of this association.

Carbohydrates

It seems that I have read this large quantitative systematic reviewand it reveals that fructose is the sweetener that will directly increase the risk of PNETs. A single 25g of fructose in your diet increases the risk of cancer by a full 22 per cent in a lifetime.[61] The excess sugar in your diet activates hyperinsulinemia, a condition that can accelerate the progression of cancer by disrupting cell cycle and blocking apoptosis and insulin-like growth factor binding protein.[62]

Lipids

Despite the lack of evidence connecting high-fat diets to PNETs, the majority of epidemiological studies show that countries with high-fat diets, especially those high in saturated fatty acids, have higher rates of PNETs.[61] When dietary fat enters the duodenum, cholecystokinin is released, stimulating pancreatic hyperplasia and making the organ more vulnerable to carcinogens.[63]

Reducing the Risk of PNETs with Diet

A major Chinese study has found that tea drinking reduced the number of PNETs by a half. [64]. However, when the consumption of fruit was reduced to twice in sennight compared to more than three times a sennight, the odds of getting PNETs were lower (OR= 1.73, 95 percent confidence interval=1.05 to 2.86), a significant protective effect. But reducing the amount of vegetables taken had the contrary effect of increasing the chances of PNETs. In conclusion, a high-fat diet, red meat, and simple carbs (mostly fructose) raise the risk of PNETs. Fruits, vegetables, and tea were found to have a PNETs - protective quality.[33]

g) Metabolic Syndrome

A clinical condition known as metabolic syndrome (MS) is linked to a higher risk of cardiovascular disease. Although there are several definitions of MS, visceral obesity, hyperglycaemia, characteristics of atherogenic dyslipidaemia, and hypertension are generally included. [65]

h) Acute Pancreatitis (AP)

A history of AP occurring one to two years before PNETs diagnosis is a recently identified risk factor for PNETs. According to a cohort study [67,68] of two Scandinavian communities, those with a history of AP were twice as likely to acquire PNETs as people without such a condition.

i) Chronic Pancreatitis (CP)

Evidence that chronic pancreatitis is a separate risk factor for pancreatic neuroendocrine tumors (PNETs) is mounting. [69] A pancreatic inflammatory disease called chronic pancreatitis causes the islet cells to be destroyed, which results in pancreatic fibrosis. [70] Rare types of pancreatic necrosis, like inherited or fibro calculous pancreatic diabetes, are more likely to develop PNET, even though the majority of pancreatitis types are linked to the highest risk of developing PNET.[71] Elderly patients and patients who had a history of chronic heavy smoking (>60 pack - years) portend a high risk of malignant transformation in chronic pancreatitis.[72]

j) Human Microflora

The human microbiota is made up of many different species, such as bacteria, viruses, fungus, and protozoa. [74] Both human health and sickness depend on them. The incidence, course, and prognosis of PNETs have been shown to be strongly correlated with the human microbiome.[75]

I Immunomodulatory action: Gut microbiota triggers a wide range of innate and adaptive immune interactions, which, in their turn, leads to tumorigenesis.[76]

II Microbial metabolites: The development of cancer cells depends on microbial metabolites like lipoteichoic acid (LTA), short-chain fatty acids (SCFAs), and secondary bile acids.[77]

III Microbiota dysbiosis: The loss of microbial diversity in the gastrointestinal system and other organ systems represents a result of the dynamic that leads to dysregulation on human microbiota which not only results in modulation of host genomic expression but also culminates in the modification of a human intrinsic immunological defense.[78].

IV Gastrointestinal microbiota: The microbial community found in the human body is primarily the gut microbiota [79]. The symbiotic relationships between its constituent bacteria play a critical role in protecting the host against infection agents by ensuring the correct physiological operation of the gastrointestinal tract. Pancreatic juice helps in supporting a healthy microbial setting by the retrograde infection prevention of the pancreas as well as possessing antibacterial actions. Pancreatic hydrolases hydrolysis is impossible without the enzymatic activity of the intestinal bacteria. There is some emerging evidence that gut microbiota could be a pathogenic agent in pancreatic neuroendocrine tumors (PNETs).[80].

V Microbial system within the pancreas: People have always believed that pancreatic microenvironment is unfriendly to bacteria colonization, since there is the secretion of very alkaline pancreatic juice and proteolytic enzymes. However, recent research using RNA probe and PCR measures has shown that bacterial density within the pancreatic tissues of patients who have pancreatic neuroendocrine tumors (PNETs) is about a thousand times higher than that which appears in the normal subjects.[81]

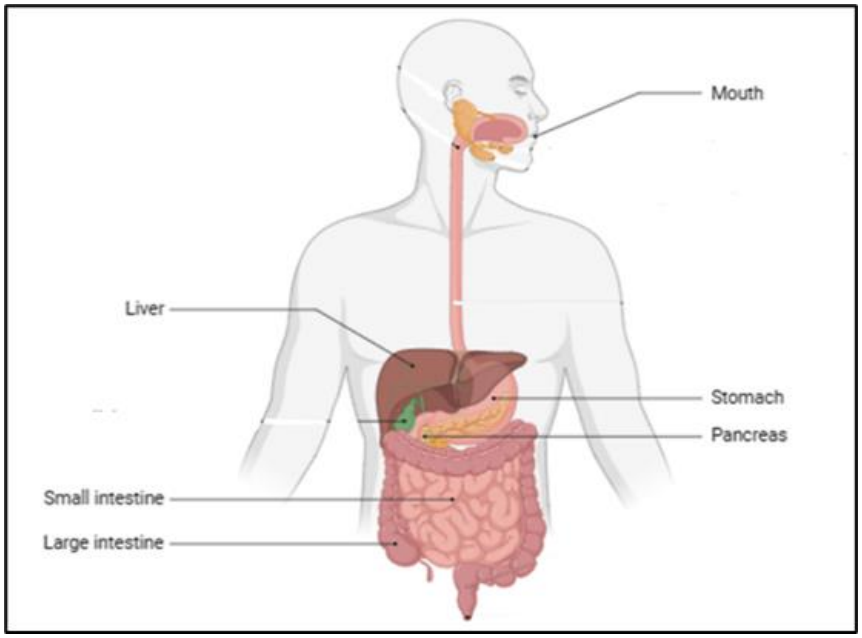

FIGURE 7: Microbial system associated with pancreatic neuroendocrine tumor.[9]

k) Infection with HBV and HCV

Recent meta-analyses [82,83] found that those with HBV (1.39 times) and HCV (1.5 times) infections were more likely to develop PNETs.

l) Periodontitis or gum disease

In the last ten years, a number of clinical investigations have found a positive association between oral cavity disease and the development of various human cancers, especially pancreatic neuroendocrine tumors.[84] Certain bacterial infections can cause periodontal diseases. Porphyromonas, Tannerella, and Actinobacillus are three types of bacteria that live in the oral cavity and are essential to the development of periodontitis.[85]

m) Occupational Exposures

The findings revealed a relative risk of 1.4 (95% CI, 1.0–1.8) for chlorinated hydrocarbon solvents and related substances and 1.9 (95% CI, 1.2–3.2) for nickel and nickel compounds. Asbestos, silica dust, organochlorine pesticides, chromium compounds, polycyclic aromatic hydrocarbons, and other chemicals were shown to have moderate but negligible risks (relative risk, 1.1; 95% CI, 0.9–1.5).[34] The daily rhythm disturbance that comes with shift work is another element that is considered and may contribute to the development of cancer.[33]

n) Cholecystectomy

A possible weak correlation between the incidence of gallstones [83], cholecystectomy [82], and PNETs risk is supported by recent epidemiological research. It's unclear why, although a slightly elevated risk of biliary tract inflammation may be the cause.[33]

3.2 NON-MODIFIABLE RISK FACTORS FOR PANCREATIC NEUROENDOCRINE TUMOR

a. Gender

According to GLOBOCAN, men have a higher incidence of pancreatic neuroendocrine tumors (5.7 per 100,000) than women (4.1 per 100,000). Women's PNETs are lower than men's. Globally, it could be because women take more steroids than men, which may protect against PNETs.[74]

b. Age

Pancreatic neuroendocrine tumor is more frequent in older persons, as is the case with most malignancies. Just 10% of instances are found before the age of 50, and its occurrence peaks between the sixth and eighth decades of life. [73]

c. Race

One important risk factor for PNETs is race. The US population is a particularly good example of how different races have different incidence rates. Black African Americans have greater PNETs incidence and fatality rates than non-Hispanic white people and other ethnic groups in every state save Hawaii. For both younger (50 years) and older people, this observation has been recorded. [33]

d. Area

Globally, PNETs prevalence varies. In the US, African Americans have a higher frequency than Caucasians, while Asian Americans and Pacific Islanders have the lowest prevalence. [68]

e. Blood Type

Large cohort research found that those with blood types A, B, and AB may be more susceptible to PNETs.[67] Genetic research has connected the ABO locus on chromosome 9q34 to PNETs risk, suggesting that those with blood type O may be less likely to develop PNETs. [66] PNETs is more

common in diabetics with blood types A, AB, or B than in those with O blood types. [52]

TABLE 3: A synopsis of PNET risk factors and risk level (in brackets)

Category	Modifiable Risk Factor of PNETs	Non-Modifiable Risk Factor of PNETs (Risk Level
Increased risk	Smoking tobacco (up to 2.5×)	Age (50–70 years old) (6.8×)
	Prolonged pancreatitis (3.0–16.0×)	Male sex (1.0–1.4×)
	High alcohol intake (up to 2.0×)	Ethnic group (Afro-Americans vs. Caucasians) (1.3×)
	Pancreatitis acute(2.0×)	Non "0" blood type (1.3–1.7×)
	diabetes mellitus Type 2 (1.5–2.0×)	
	Obesity—per 5 kg/m2 (1.1×)	
Reduced risk	Tea consumption (0.5×)	
	Fruitarian diet (0.6×)	
	Hay fever (0.6×)	

3. SIGN AND SYMPTOMS

FIGURE 8: showing signs and symptoms involved in PNETs. [50]

4. PATHOGENESIS

5.1 Pathology of Pancreatic neuroendocrine tumor

arly detection of non-invasive pre-cancerous lesions in the pancreas, when treated, may lead to developing a low number of pancreatic neuroendocrine tumors (PNETS). Precancerous lesions are classified as either small or large based

on how close they are located to the ductal system of the pancreas. Most PNETs are very small. Pancreatic Intraepithelial Neoplasias (PanIN) is a type of ductal tumor of the pancreas.[10]

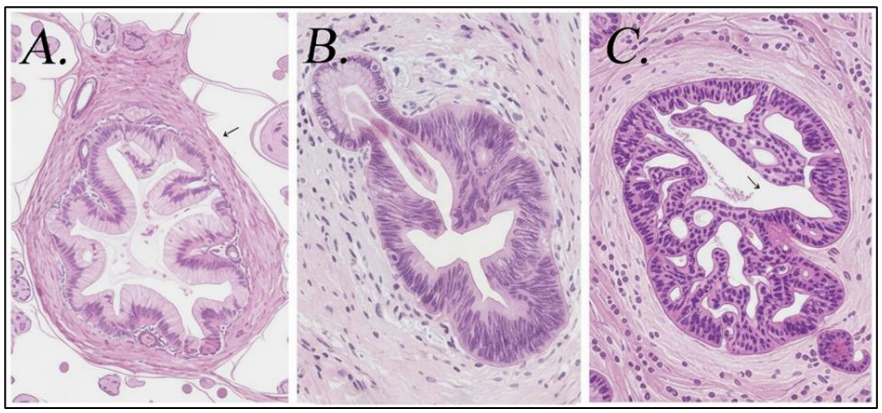

FIGURE 9: pancreatic precancerous tumour. (A) The pancreatic ducts are affected by low-grade PanINs. They have modest cytologic atypia, apical mucin, and polarity-preserving nuclei. (B) Increased cytologic and architectural atypia, such as loss of nuclear polarity, nuclear pleomorphism, and architectural complexity, are characteristics of high-grade PanIN.(C) Invasive PNETs has a remarkable desmoplastic reaction in the stroma together with severe architectural and cytologic atypia.

These lesions can be categorized based on cytologic and architectural atypia into low-grade and high-grade categories (see Figure 9). The current classification system uses a two-tiered approach in terms of grade of pancreatic precursor lesions (i.e., low-grade vs. high-grade) rather than the previously used three-tiered approach. Low-grade lesions typically demonstrate basally-oriented nuclei with mild to moderately atypical cytology; high-grade lesions demonstrate significantly altered architecture (cribriforming, micro-papillae formation, budding); severely atypical cytology; and loss of nuclear orientation (See Figure 9A).[10]

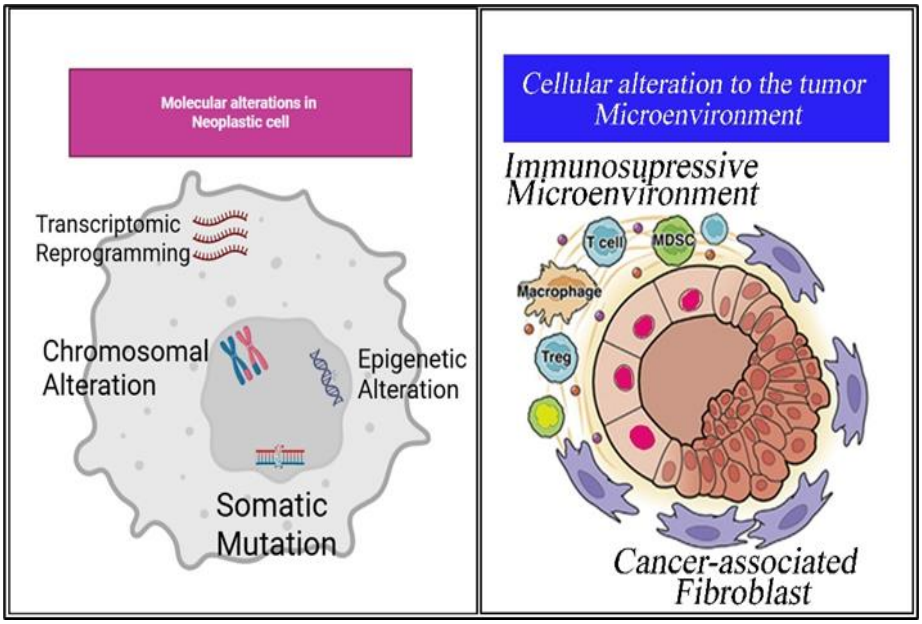

FIGURE 10: The pathologic process leading to pancreatic neuroendocrine tumors involve a variety of molecular contributors, at the level of the tumor cell itself (e.g., mutations in "driver" genes;

chromosomal changes; epigenetic changes; and transcriptional reprogramming) and also at the cellular level through other components of the non-neoplastic tumor micro-environment (e.g., changes in the immune micro-environment and changes in cancer associated fibroblasts). Examples of population level contributors include chronic pancreatitis, inherited mutations in DNA, obesity, diabetes, and smoking.

5.2 Molecular Alterations in Myeloma Cells

At least some of the molecular changes seen in PNET malignant cells can be attributed to mutations in oncogenes and tumor-suppressor genes (Fig. 10). The molecular genetic and sequencing techniques used in the early 1980s and 1990s to identify the most commonly mutated genes in PNETs found KRAS an oncogene and CDKN2A, TP53, and SMAD4 tumor suppressors [48]. Chromothripsis is a process derived from the Greek words "chro" (chromosome) and "thripsis" (shattering), in which hundreds of clustered genomic rearrangements happen on one chromosome or a few. This may have occurred due to catastrophic events of DNA damage and resulted in a punctuated evolutionary process rather than a continuous evolutionary process.[44]

5.3 Cellular Alterations to the Tumour Microenvironment

In addition to the significant molecular alterations in neoplastic cells that have been previously documented, interactions with non-neoplastic cells in the tumor microenvironment also have a significant impact on pancreatic carcinogenesis. (Figure 10).[10]

5. DIAGNOSIS

6.1 CHALLENGES IN EARLY DETECTION

Early identification is one of the most difficult aspects of managing pancreatic neuroendocrine tumor. Abdominal discomfort, weight loss, and jaundice are common non-specific symptoms of the illness that are usually signs of severe disease. The cancer has typically spread by the time these symptoms manifest, making curative therapy challenging. [44] The public does not yet have access to any reliable screening tests. Imaging methods like magnetic resonance imaging (MRI) or endoscopic ultrasound (EUS) may be used on a regular basis to monitor high-risk individuals, such as those with a known genetic mutation or a family history of pancreatic neuroendocrine tumor. But these techniques are costly, intrusive, and not commonly accessible.[41]

6.2 IMAGING TECHNIQUES

For the diagnosis and staging of pancreatic neuroendocrine tumors, imaging is essential. EUS, magnetic resonance imaging (MRI), and computed tomography (CT) scans are the most commonly used modalities. CT scans are commonly used as the first imaging test because of their ease of use and effectiveness in detecting pancreatic masses and assessing their resectability.[41] MRI has superior soft tissue contrast when compared to CT, and it is particularly useful for detecting small lesions and assessing liver metastases. Diffusion-weighted imaging (DWI), a particular MRI technique, enhances the detection of small lesions by monitoring the movement of water molecules across tissues.[40]

6.3 MOLECULAR DIAGNOSTICS AND BIOMARKERS

Biomarkers are chemicals that may be detected in tissues, urine, or blood to show whether cancer is present. About 80% of individuals with pancreatic neuroendocrine tumor have high levels of the carbohydrate antigen CA 19-9, which is the most often utilised biomarker for the disease. But CA 19-9 is not exclusive to pancreatic neuroendocrine

tumor; it can also be increased in cirrhosis, cholangitis, and other gastrointestinal malignancies. Rather than being useful for early diagnosis, it is mostly useful for tracking therapy response and identifying illness recurrence. [32]

6. TREATMENT

7.1 PREOPERATIVE PREPARATION

High morbidity and mortality are linked to surgical excision of PNETs, either distal pancreatectomy (DP) with splenectomy or pancreaticoduodenectomy (PD). Therefore, to prevent difficulties, careful preoperative planning is crucial. Patients with pancreatic head cancer may experience obstructive jaundice. [1] Improvements in the patient's general health and liver function are associated with preoperative drainage. One of the main negative effects is the entry of infection into the biliary tree, though.[28]

We look forward to the findings of ongoing research projects like NCT02562716, NorPACT-1, NEOPAC, and NEPAFOX. Neoadjuvant chemoradiotherapy is a successful treatment for resectable PNETs, as several trials have shown. [110, 111]

7.2 SURGICAL INTERVENTIONS

The emphasis has shifted to completing the treatments using minimally invasive techniques since the mortality and morbidity rates associated with pancreatic surgery have declined over the past few decades. The emphasis has shifted to completing the treatments with minimally invasive techniques since pancreatic surgery mortality and morbidity rates have decreased in last some decennary.[1]

One of the most feared consequences of Parkinson's disease is post-operative pancreatic fistula (POPF).[126] The kind of pancreatoenteric anastomosis is the first of several strategies that have been promoted to lower its incidence. Pancreaticogastrostomy has been linked to a lower incidence of POPF, according to many randomised control trials (RCTs) and meta-analyses.[26] However, because pancreatojejunostomy (PJ) is more physiological and has fewer long-term problems than pancreaticogastrostomy, it is the method that is most used. [25]

7.3 NEOADJUVANT THERAPY

According to current guidelines, chemotherapy ± chemoradiation is initiated for borderline and locally progressed lesions. If the patient is performing well, Currently, 5 5-Fluorouracil, Irinotecan, and Oxaliplatin (FOLFIRINOX) ± chemoradiation is advised.[1] Gemcitabine and nab-paclitaxel ± chemoradiation are additional options. According to recent research, radiological regression is not as good a predictor of response as lowering CA19-9 levels and the absence of disease progression following neoadjuvant treatment. [24] Research on the significance of neoadjuvant therapy in resectable lesions of PNETs has been prompted by the promising outcomes of neoadjuvant and perioperative chemoradiation treatments in oesophageal, gastric, and rectal cancer.[1]

The outcomes of ongoing studies like NCT02562716, NorPACT-1, NEOPAC, and NEPAFOX are eagerly anticipated. Neoadjuvant chemoradiotherapy is a successful treatment for resectable PNETs, as several trials have shown.[23]

7.4 ADJUVANT THERAPIES

The advantages of chemotherapy over chemoradiotherapy have been demonstrated by the ESPAC-1 study. [22] Following the CONKO-1 trial's demonstration of gemcitabine's effectiveness in adjuvant chemotherapy, 5-

fluorouracil (5-FU) was replaced with gemcitabine-based regimens. [21] The standard regimen for adjuvant treatment is currently the combination of gemcitabine and capecitabine, as demonstrated by the ESPAC-4 study. [20]

7.5 RADIATION THERAPY AND CHEMOTHERAPY

Chemotherapy is still the cornerstone of care for patients with pancreatic neuroendocrine tumor that has spread or is incurable. The most popular regimens are FOLFIRINOX and gemcitabine with nab-paclitaxel; because of its greater toxicity profile, FOLFIRINOX is often saved for patients with good performance status. Although the median survival has increased to around 11–12 months because of these regimens, the overall prognosis is still not good.[14] Radiation therapy is used in some circumstances, primarily for locally advanced diseases when the tumor is incurable but has not spread. It is often used in combination with chemotherapy (chemoradiation) to enhance the therapeutic effect.[16]

A new method called stereotactic body radiation treatment (SBRT) exposes surrounding tissues to high radiation doses over a few sessions. In patients with locally advanced pancreatic neuroendocrine tumor, SBRT has shown potential in improving quality of life and slowing the growth of local tumors. [15]

7. CONCLUSION

Given its mysterious character, aggressive biology, and consistently dire statistics, pancreatic neuroendocrine tumor's moniker as "the silent killer" is regrettably well-deserved. The greatest effect will come from prevention, early identification, and customised multidisciplinary care, even though the previous ten years have seen some advancements in our understanding of the illness and its risk factors, as well as incremental advancements in novel medications. To improve the prognosis for patients in the future, more studies into molecular pathways, the gut microbiota, genetic indicators, and innovative treatments are essential. Reducing modifiable risks, increasing professional and public awareness, and accelerating diagnostic innovation are all critical to improving the outcomes of pancreatic neuroendocrine tumors.

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HOW TO CITE: Krushna Tidke*, Dhanshree Mande, Ajinkya Vaidya, Dr. Nilesh Chachda, "The Silent Killer": A Comprehensive Review of Pancreatic Neuroendocrine Tumor, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 11, 3441-3464 https://doi.org/10.5281/zenodo.17678335