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Pancreatic Cancer: Diagnosis and Management

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Abstract:*Pancreatic adenocarcinoma has high prevalence and mortality. Disease is more common in individuals over 70 and rarely occurs before the age of 40.Contributory factors for pancreatic cancer include advance age, male gender, more common in African American than African in their native Africa, smoking, obesity, family history, chronic pancreatitis, diabetes mellitus, red and processed meat, and strong evidence with heavy drinking. Pancreatic Adenocarcinoma (exocrine type cancer) are more common than neuroendocrine type cancer. In the early stages there are no symptoms of the disease. Pain in the upper stomach, jaundice, unexplained weight loss, tumor may compress neighboring organs, and 50% of patients with pancreatic adenocarcinoma also have diabetes. Diagnosis by medical imaging. Treatment with surgery, radiotherapy, chemotherapy and palliative care. Prevention, not smoking, limiting the intake of red and processed meat, healthy weight, and consumption of fruits and vegetables. Early detection and treatment have better outcome.*

Keywords: *Adenocarcinoma, non-endocrine cancer, Management, Prognosis,*

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I. Introduction

In 2015,there were 393,800 reported cases and 411,600 deaths globally due to pancreatic cancer[1,2].The most common, pancreatic adenocarcinoma, accounts for about 85% of cases, and the term "pancreatic cancer "is sometimes used to refer to that type [3].Several other types of cancer, which collectively represent the majority of the non-adenocarcinomas, can also arise from these cells[3,].One to two percent of cases of pancreatic cancer are neuroendocrine tumors, which arise from the hormone producing cells of pancreas[3].These are generally less aggressive than pancreatic adenocarcinoma [3].Pancreatic cancer rarely occurs before the age of 40,and more than half the cases of pancreatic adenocarcinoma occur in those over 70[4] Risk factors for pancreatic cancer include tobacco smoking, obesity, diabetes, and certain rare genetic conditions[4].Signs and symptoms of most common form of pancreatic cancer may include yellow skin, abdominal or back pain ,unexplained weight loss, light colored stool, dark urine and loss of appetite[5].There are usually no symptoms in the disease's early stages, and symptoms that specific enough to suggest pancreatic cancer typically do not develop until the disease has reached the an advanced stage[5,6].By the time of diagnosis, pancreatic cancer has often spread to other parts of the body[3].Diagnosis by the medical imaging, such as ultrasound or computed tomography, blood tests and examination of tissue samples(biopsy)[7].Disease is divided into stages, from early stage(stage 1) to late stage(stage IV).[8].Treatment with surgery, radiotherapy, chemotherapy, and palliative care [5]. Treatment option are partly based on cancer stage [5].Prevention, avoid smoking, maintaining a healthy weight,and limiting the consumption of red or processed meat[9].Paper provides current notions on the diagnosis, and management of pancreatic cancer.

II. Historical Perspectives

The earliest recognition of pancreatic cancer has been attributed to the 18th century Italian scientist Giovanni Battista Morgagni,the historical father of modern-day anatomic pathology, who claimed to have traced several cases of cancer in the pancreas. Many 18th and 19th-century physicians were skeptical about the existence of the disease, given the similar appearance of pancreatitis. Some case reports were published in the 1820s and 1830s, and a genuine histological diagnosis was eventually recorded by the American clinician Jacob Mendes Da Costa, who also doubted the reliability of Morgagni'sinterpretations. By the 20thcentury, cancer of the head of pancreas had become a well-established diagnosis [10]Regarding the recognition of PanNETs, the

possibility of cancer of the islet cells was initially suggested in 1888.The first case of hyperinsulinism due to a tumor of this type was reported in 1927.Recognition of a non-insulin-screening type of Pan NETs is generally ascribed to the American surgeons, RM Zollinger and EH Ellison, who gave their names to Zollinger-Ellison syndrome after postulating the existence of a gastrin-screening tumor in a report of two cases of unusually severe peptic ulcers published in 1955[10].In 2010,the WHO recommended that PanNETs be referred to as ”neuroendocrine “rather than ”endocrine” tumors[11].

In 1912 the German surgeon Walther Kausch was first to remove large parts of the duodenum and pancreas together (en bloc).In 1918 it was demonstrated in operations on dogs that total removal of the duodenum is compatible with life, but this was not reported in human surgery until 1935,when the American surgeon Allen Old father Whipple published the results of a series of three operations at Columbia Presbyterian Hospital in New York. Only one of the patients had the duodenum totally removed, but he survived for two years before dying of metastasis to the liver. The operation was unplanned, as cancer was discovered in the operating theater.Whipple's success showed the way for the future, but operation remained a difficult and dangerous one until recent decades. He published several refinements to his procedure, including the first total removal of duodenum in 1940, but he only performed a total of 37 operations [10].The discovery in the late 1930s that vitamin K prevented bleeding with jaundice, and the development of blood transfusion as an everyday process, both improved post-operative survival [10],but about 25% of people never left hospital alive as late as the 1970s[12].In the 1970s a group of American Surgeons wrote that procedure was too dangerous and should be abandoned. Since then outcomes in larger centers have improved considerably, and mortality from operation is often less than 4%[13].In 2006 a report was published of a series of 1,000 consecutive pancreaticoduodenectomies performed by a single surgeon from John Hopkins Hospital between 1969 and 2003.the rate of these operations had increased steadily over this period, with only three before 1980, and the median operating time reduced from 8.8 hours in the 1970s to 5.5 hours in 2000s, and mortality within 30 days or in hospital was 1%[10,12]Another series of 2,050 operations at the Massachusetts General Hospital between 1941 and 2011 showed a similar picture of improvement[14].

Small precancerous neoplasms for many pancreatic cancers are being detected at greatly rates by modern medical imaging. One type, intraductal papillary mucinous neoplasm (IPMN) was first described by a Japanese researchers in 1982.It was noted in 2010 that "For the next decade, littleattention was paid to this report; however, over the subsequent 18 years, there has been a virtual explosion in the recognition of this tumor [15].

III. Contributory Factors

Contributory or risk factors for pancreatic cancer include:[6,3].

- Age,gender and ethinicity plays an important role, advance age, male gender and ethnicity e.g.more common in African American than African in their native Africa,
- Smoking cigarette is the best-established avoidable risk factor. The risk declines slowly after smoking cessation, taking some 20 years to return to almost of non-smokers [16].
- Obesity, a BMI greater than 35 increases relative risk by about half [17].
- Family history;5-10% of pancreatic cancer cases have an inherited component. Risk increases with first degree relative had the disease. The risk increases to 30-40 % to age of 70[7].Screening for early pancreatic cancer may be offered to individuals with hereditary pancreatitis on a research basis [18,].
- Chronic pancreatitis appears to almost triple risk, and as with diabetes, new onset pancreatitis may be symptoms of tumor [7].The risk of pancreatic cancer in individuals with familial pancreatitis particularly high[19].
- Diabetes mellitus is a risk factor for pancreatic cancer. People who have been diagnosed with type-2 diabetes for longer than ten years may have 50% increased risk, as compared with non-diabetic [7].
- Specific type of food have not been clearly shown to increase the risk of pancreatic cancer[6].Processed meat, red meat and meat cooked at very high temperature(e.g.by frying, broiling or barbecuing, shown to have slightly increased risk[20].
- Alcohol consumption excessively is a major cause of pancreatitis, which in turn predisposes to pancreatic cancer. Research has failed to firmly establish alcohol consumption as adirect risk factors for pancreatic cancer. Evidence is stronger for a link with heavy drinking of at least six drinks per day[7,21].

IV. Type of Pancreatic Cancer

The vast majority of cases (about 99%) occur in the part of pancreas which produces digestive enzymes, known as exocrine component. There are several sub-types of exocrine pancreatic cancers, but their diagnosis and treatment have much in common. The small minority of cases that arise in the hormone producing (endocrine) tissue of the pancreas have different clinical characteristics. Both groups occur mainly (but not

exclusively) in people over 40, and are slightly more common in men, but sub rare sub-types mainly occur in women and or children [22].

Exocrine type cancers: The exocrine group is dominated by pancreatic adenocarcinoma(variations of this name may add "invasive "and "ductal")which is far most common type, representing about 85% of all pancreatic cancers[6]. Nearly all of these start in the ducts of the pancreas, as pancreatic ductal adenocarcinoma (PDAC)[23].This is despite the fact that the tissue from which arise-the pancreatic ductal epithelium-represents less than 10% of the pancreas by cell volume, because it constitutes only the ducts(an extensive but capillary-like duct-system fanning out)within the pancreas[13].This cancer originates in the ducts that carries secretions(such as enzymes and bicarbonate) away from the pancreas. About 60-70% of adenocarcinoma occur in the head of the pancreas[6].Other type of exocrine cancer includes: carcinoma arise in the clusters of cells that produce enzymes, and represents 5% of exocrine pancreas cancers[24],Cystadenocarcinomas account for 1% of pancreatic cancers, and they have better prognosis than other exocrine types[24],Pancreatoblastoma is a rare form, mostly occurring in childhood, and with relatively good prognosis[6,25],and Pancreatic mucinous cystic neoplasm are broad group of pancreas tumors that have various malignant potential. They are being detected at a greatly increased rates at CT scans become more powerful and common, and discussion continues as how best to assess and treat them, given that many are benign[26].

Neuroendocrine type cancer: The small minority of tumors that arise elsewhere in the pancreas are mainly pancreatic neuroendocrine tumors(PanNETs)[11].Neuroendocrine tumors (NETs) are a diverse group of benign or malignant tumors that arise from the body's neuroendocrine cells, which are responsible for integrating the nervous and endocrine systems. Nets can start in most organs of the body, including the pancreas, where the various malignant types are considered to be rare.PanNETs are grouped into"functioning" and' non-functioning 'types, depending on the degree to which they produce hormones. The functioning types secrete hormones such as insulin, gastrin, and glucagon into blood stream, often in large quantities, giving rise to serious symptoms such as low blood sugar, but also favoring relatively early detection. The most common functioning PanNETs are insulinomas, named after the hormones they secrete. The non-functioning types do not secrete hormones in a sufficient quantity to give rise to overt clinical symptoms. For this reason, on-functioning PanNETS are often diagnosed only after the cancer has spread to other parts of the body [27].As with other neuroendocrine tumors, the history of the terminology and classification of PanNETs is complex [27].PanNETs are sometimes called "Islet cell cancers"[28], even though it is now known that they do not actually arise from islet cells as previously thought[27].

V. Clinical Manifestations

Pancreatic cancer usually does not cause recognizable symptoms in its early stages, the disease is typically not diagnosed until it has spread beyond pancreas itself [4].This is one of the main reasons for generally poor survival rates. Exceptions to this are the functioning PanNETs where over production of various active hormones can give rise to symptoms(which depend on the type of hormone)[29].Bearing in mind that disease is rarely diagnosed before the age of 40,common clinical manifestations of pancreatic adenocarcinoma occurring before diagnosis include:

a).Pain in the upper stomach or back, often spreading from around the stomach to the back. The location of the pain can indicate the part of the pancreas where a tumor is located. The pain may be worse at night and may increase over time to become severe and unremitting [24].In the UK, about half of new cases of pancreatic cancer are diagnosed following a visit to a hospital emergency department for pair or jaundice. In up to two-thirds of people abdominal pain is the main symptom, for 46% of total accompanied by jaundice, with 13% having jaundice without pain [17].

b).Jaundice, a yellow tint to the white of the eyes or skin, with or without pain, and possibly in combination with darkened urine. This results when a cancer in head of the pancreas obstructs the common bile duct as it runs through the pancreas [30].

c).Unexplained weight loss either from loss of appetite, or loss of exocrine function resulting in poor digestion [17].

d).The tumor may compress neighboring organs, disrupting digestive process and making it difficult for the stomach to empty, which may cause nausea and a feeling of fullness. The undigested fat leads to foul-smelling fatty feces that are difficult to flush away [17].Constipation is common [31].

e).At least 50% of people with pancreatic adenocarcinoma have diabetes at time of diagnosis [6].While long standing diabetes is known risk factor for pancreatic cancer, the cancer can itself cause diabetes, in which case recent onset of diabetes could be considered an early sign of the disease [32].People who develop diabetes have eight times the usual risk of developing pancreatic adenocarcinoma within three years, after which the relative risk declines [17].

Miscellaneous symptoms

- Trousseau syndrome, in which blood clots form spontaneously in the portal blood vessels, the deep veins of extremities, or the superficial veins anywhere on the body, may be associated with pancreatic cancer, and is found in about 10% of cases[7].
- Clinical depression has been reported in association with pancreatic cancer in some 10-20% of cases, and can be a hindrance to optimal management. The depression sometimes appears before the diagnosis of cancer, suggesting that it may be the biology of the disease [7].
- Other common manifestations of the disease include: weakness and tiring easily,dry mouth, sleep problems; and a palpable abdominal mass [31].

Metastasis

The spread of pancreatic cancer to other organs may also cause symptoms. Typically, pancreatic cancer first spreads to nearby nodes, and later to the liver or to the peritoneal cavity, large intestine or lungs[7].It is uncommon for it to spread to bones or brain[33].Cancers in pancreas may also be secondary cancers that have spread from other parts of the body. This is uncommon, found in only about 2% of cases of pancreatic cancer. Kidney cancer is by far the most common cancer to spread to the pancreas, followed by colorectal cancer, and then cancers of the skin, breast, and lung. Surgery may be performed in such cases, whether in hope of a cure or to alleviate symptoms [34].

VI. Diagnosis

Regardless of a tumor's location, the most common symptom is unexplained weight loss, which may be considerable. A large minority (between 35% and 47%) of people diagnosed with the disease have nausea, vomiting or feeling of weakness. Tumors in the head of the pancreas typically also cause jaundice, pain, loss of appetite, dark urine, and light colored stools. Tumors in the body and tail typically also cause pain[30].People sometimes have recent onset of atypical type 2 diabetes that is difficult to control, a history of recent but unexplained blood vessel inflammation caused by blood clots (thromobophelibitis) known Trousseau sign or recent attack of pancreatitis[30].Abdominal ultrasound is less sensitive and will miss small tumors, but can identify cancers that have spread to the liver and build-up of fluid in the peritoneal cavity (ascites)[17].It may be used for a quick and cheap first examination before other techniques[35].Medical imaging techniques, such as computed tomography(CT scan) and endoscopic ultrasound(EUS) are used to confirm the diagnosis and help decide whether the tumor can be surgically removed(its"resectability"),[17].Magnetic resonance imaging(MRI) and position emission tomography may also be used[6].Endoscopic retrograde cholangiopancreatography(ERCP) and percutaneous trans hepatic cholangiography have replaced i.v.cholangiograms [36].

Pancreatic cancer staging,(Exocrine cancers):Pancreatic cancer is usually staged following CT scan[30].The most widely used cancer staging system for pancreatic cancer is the one formulated by the American Joint Committee on Cancer(AJCC) together with the Union for International Cancer Control(UINCC}.The AJCC-UICC staging system designate four main overall stages from early to advanced disease, based on TNM classification of Tumor size,spread to lymph Nodes and Metastasis [37].

PanNETs:The 2010 WHO classification of tumors of the digestive system grades all the pancreatic neuroendocrine tumors (PanNETs) into three categories, based on their degree of cellular differentiation (from "NET GI" through to the poorly differentiated :NET G3"[38,].The U.S.National Comprehensive Cancer Network recommends use of the same AJCC-UICC staging system as pancreatic adenocarcinoma[39,37].Using this scheme, the stage by –stage-stage outcomes for PanNETs are similar to those endocrine cancers[40].A different TNM system for PanNETs has been proposed by the European Neuroendocrine Tumor Society[38].

VII. Management and Prognosis

The final assessment after diagnosis in exocrine cancer is whether surgical removal of the tumor is possible as this is the only cure for this cancer. Whether or not surgical resection can be offered depends on how much the cancer has spread[7].Chemotherapy and, to lesser extent, radiotherapy are likely to be offered to most people, whether or not surgery is possible. Specialist advise that the management of pancreatic cancer should be in the hands of a multidisciplinary team, and best conducted in larger centers [6,7].

Surgery: Surgery with intention of a cure is only possible in around one-fifth(20%) of new cases[17].Although CT scans help, in practice it can be difficult to determine whether the tumor can be fully removed(its:resectability"),and it may become apparent during surgery that it is not possible to successfully remove the tumor without damaging other vital tissues[6].Even when the operation appears to have been successful, cancerous cells are often found around the edges("margins") of the removed tissue. When a pathologist examines them microscopically, indicating the cancer has not been entirely removed [6].

Although curative surgery no longer entails very high death rates that occurred until 1980s,a high proportion of people(about 30-45%) still have to be treated for a post-operative sickness that is not caused by the cancer itself. The most common complications of surgery is difficulty in emptying the stomach [7].**Chemotherapy**: After surgery, adjuvant chemotherapy with gemcitabine or 5-FU can be offered if the person is sufficiently fit, after a recovery period of one to two months[4,35].The FOLFIRINOX chemotherapy regimen using four drugs was found more effective than gemcitabine, but with substantial side effects, and thus only suitable for people with good performance status[41].However, the changes of the last few years have only increased survival times by a few months[42].Clinical trials are often conducted for novel adjuvant therapy[4].

Radiotherapy: The role of radiotherapy as an auxiliary(adjuvant) treatment after potentially curative surgery has been controversial since the 1980s[7].The European Society for Medical Oncology recommends that adjuvant radiotherapy should only be used for people enrolled in clinical trials[9].Radiotherapy may form part of treatment to attempt to shrink a tumor to a resectable state, but its use on unreectable tumors remains controversial as there are conflicting results from clinical trials. The preliminary results of one trial, presented in 2013,"markedly reduced enthusiasm" for its use on locally advanced tumor [6].

PanNETs:Treatment of PanNETs including the less common malignant types, may include a number of approaches that include:[39,43,44].

a). Small tumors of less than 1 cm. that are identified accidently for example on a CT scan performed for other purposes, may be followed watchful waiting [39].Tumors within the pancreas only (localized tumors),or with limited metastasis, for example to the liver, may be removed by suegery.The type of surgery depends on the tumor location, and the degree of spread to lymph nodes[38].

b). Localized tumors:The surgical procedure may be much less extensive than the types of surgery used to treat pancreatic adenocarcinoma, but otherwise surgical procedures are similar to those for exocrine tumors[38].Use of liver transplantation may be considered in certain cases of liver metastasis[45].

c). Functioning tumors:The somatostatin analog class of medications,such as ocreotide,can reduce the excessive production of hormones[38].Lanreotide can slow tumor growth[46].Standard cytotoxic chemotherapy is generally not very effective for PanNETs,but may be used when other drug treatments fail to prevent the disease from progressing[27,47,85].

Prognosis: Pancreatic adenocarcinoma and other less common exocrine cancers have a very poor prognosis, as they are diagnosed at a late stage when cancer is already locally advanced or has spread to other parts of the body. Outcomes are better much better for PanNETs:many are benign and completely without clinical symptoms, and even those cases not treatable with surgery have an average five-year survival rate of 16%[48],although outlook varies considerably according to the type[29].In less than 20% of cases of pancreatic adenocarcinoma with a diagnosis of a localized and small cancerous growth(less than 2 cm in Stage 1),about 20% of Americans survive to five years[49].

VIII. Palliative Care and Prevention

Palliative care focuses not on treating the underlying cancer, but on treating symptoms such as pain or nausea, and assist in decision-making, including when or if hospice care will be beneficial[50].Pain can be managed with medications such as opioids or through procedural intervention, by a nerve block on the celiac plexus(CPB)[7].Both surgery and advanced inoperable tumors often lead to digestive system disorders from a lack of the exocrine products of pancreas(exocrine insufficiency).These can be treated by taking pancreatin which contains manufactured enzymes and is best taken with food[17].Difficulty in emptying the stomach(delayed gastric emptying) is common and can be serious problem,involvinghospitalization, nasogastric aspiration and medication(proton pump inhibitors or H2 antagonistic)[17].

Prevention: Apart from not smoking, the American Cancer Society recommends keeping a healthy weight, and increasing consumption of fruits, and vegetables, and whole grains, while decreasing consumption of red and processed meat. Although there is no consistent evidence this will prevent or reduce pancreatic cancer specifically[51].A 2014 review of research concluded that there was evidence that consumption of citrus fruits and curcumin reduced risk of pancreatic cancer, while there was possibility a beneficial effect from whole grains, foliate, selenium, and non-fried fish[21].General population screening not considered effective, nevertheless, regular screening with endoscopic ultrasound and MRI/CT imaging is recommended for those at high risk from inherited genetics [4, 35, 52].

IX. Conclusions

Pancreatic cancer has high mortality worldwide. Early detection,surgery, radiotherapy or chemo therapy have better outcome. Prevention include, not smoking, high fruit and vegetable intake, and decreasing consumption of red and processed meat.

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