SCIENTIFIC RESEARCH CENTER

International Journal of Social Science and Humanities Research
Vol. 6, No. 4, 2018, pp. 1-26.

ISSN 2348-2990

International Journal of Social Science and Humanities Research

www.scientificrc.com

https://scientificrc.com/journals/international-journal-of-social-science-and-humanities-research/volume-6-issue-4-october-december-2018/Pancreatic Cancer on Occasion of November: Pancreatic Cancer Awareness Month

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Abstract

The pancreas is a pear-shaped gland located in the abdomen between the stomach and the spine. Exocrine and endocrine are the two components of pancreas. The exocrine component is made up of ducts and small sacs called acini on the end of the ducts. This part of the pancreas makes specialized proteins called enzymes that are released into the small intestine to help the body digest and break down food, particularly fats. The endocrine component of the pancreas is made up of cells lumped together in different locations within this part of the pancreas, called islets of Langerhans. These cells make specific hormones, most importantly insulin. Insulin is the substance that helps control the amount of sugar in the blood. This portion of the pancreas also makes other hormones, such as glucagon, somatostatin, pancreatic polypeptide (PP), and vasoactive intestinal peptide (VIP). Each of these hormones plays an important role in regulating the body's metabolism. Pancreatic cancer arises when cells in the pancreas, a glandular organ behind the stomach, begin to multiply out of control and form a mass. These cancerous cells have the ability to invade other parts of the body. The month November marks Pancreatic Cancer Awareness Month, a time when people across the world come together to fight back against, and raise the profile of, pancreatic cancer. The World Pancreatic Cancer Day is being celebrated on 15 November. The day stresses the need for better diagnostic methods for the early detection of pancreatic cancer. Early detection could improve outcomes for patients with the cancer. It is a time of the year when people have the most voices speaking out the disease, raising funds for early diagnosis research and raising awareness in their local communities. Signs and symptoms of the most common form of pancreatic cancer may include yellow skin, abdominal or back pain, unexplained weight loss, light-colored stools, dark urine and loss of appetite. Worldwide efforts on many levels are underway to understand pancreatic cancer, but progress has been slow, particularly into understanding the disease's causes. There are several fundamental unanswered questions.

Keywords: PanNETs; Pancreatoblastoma; Infography; Staging; Pancreatic Cancer Day.

INTRODUCTION

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. These contrast with benign tumors, which do not spread to other parts of the body.[8] Possible signs and symptoms include a lump, abnormal bleeding, prolonged cough, unexplained weight loss and a change in bowel movements. While these symptoms may indicate cancer, they may have other causes. Over 100 types of cancers affect humans. Tobacco use is the cause of about 22% of cancer deaths. Another 10% are due to obesity, poor diet, lack of physical activity or excessive drinking of alcohol. Other factors include certain infections, exposure to ionizing radiation and environmental pollutants. In the developing world, 15% of cancers are due to infections such as Helicobacter pylori, hepatitis B, hepatitis C, human papillomavirus infection, Epstein–Barr virus and human immunodeficiency virus (HIV). These factors act, at least partly, by changing the genes of a cell. Typically, many genetic changes are required before cancer develops. Approximately 5–10% of cancers are due to inherited genetic defects from a person's parents. Cancer can be detected by certain signs and symptoms or screening tests. It is then typically further investigated by medical imaging and confirmed by biopsy (Jayasekara, *et al*, 2016).
Many cancers can be prevented through remaining away from smoking, maintaining a healthy weight, not drinking too much alcohol, eating plenty of vegetables, fruits and whole grains, vaccination against certain infectious diseases, not eating too much processed and red meat and avoiding too much sunlight exposure. Early detection through screening is useful for cervical and colorectal cancer. The benefits of screening in breast cancer are controversial. Cancer is often treated with some combination of radiation therapy, surgery, chemotherapy and targeted therapy. Pain and symptom management are an important part of care. Palliative care is particularly important in people with advanced disease. The chance of survival depends on the type of cancer and extent of disease at the start of treatment. In children under 15 at diagnosis, the five-year survival rate in the developed world is on average 80%. For cancer in the United States, the average five-year survival rate is 66% (Parkin, *et al, 2011;* Kushi, *et al, 2012).*

In 2015, about 90.5 million people had cancer. About 14.1 million new cases occur a year (not including skin cancer other than melanoma). It caused about 8.8 million deaths (15.7% of deaths). The most common types of cancer in males are lung cancer, prostate cancer, colorectal cancer and stomach cancer. In females, the most common types are breast cancer, colorectal cancer, lung cancer and cervical cancer. If skin cancer other than melanoma were included in total new cancer cases each year, it would account for around 40% of cases. In children, acute lymphoblastic leukemia and brain tumors are most common, except in Africa where non-Hodgkin lymphoma occurs more often. In 2012, about 165,000 children under 15 years of age were diagnosed with cancer. The risk of cancer increases significantly with age, and many cancers occur more commonly in developed countries. Rates are increasing as more people live to an old age and as lifestyle changes occur in the developing world. The financial costs of cancer were estimated at $1.16 trillion USD per year as of 2017 (Vitthalrao Bhimasha Khyade, 2018). There are about 120 different types of cancers are reported. Cancers are classified generally on the basis of organ to which it concern. Pancreatic cancer arises when cells in the pancreas, a glandular organ behind the stomach, begin to multiply out of control and form a mass. These cancerous cells have the ability to invade other parts of the body.

There are a number of types of pancreatic cancer. The most common, pancreatic adenocarcinoma, accounts for about 85% of cases, and the term "pancreatic cancer" is sometimes used to refer only to that type. These adenocarcinomas start within the part of the pancreas which makes digestive enzymes. Several other types of cancer, which collectively represent the majority of the non-adenocarcinomas, can also arise from these cells. One to two percent of cases of pancreatic cancer are neuroendocrine tumors, which arise from the hormone-producing cells of the pancreas. These are generally less aggressive than pancreatic adenocarcinoma (GBD, 2015 ; Vitthalrao B. Khyade, 2018). Signs and symptoms of the most common form of pancreatic cancer may include yellow skin, abdominal or back pain, unexplained weight loss, light-colored stools, dark urine and loss of appetite. There are usually no symptoms in the disease's early stages, and symptoms that are specific enough to suggest pancreatic cancer typically do not develop until the disease has reached an advanced stage. By the time of diagnosis, pancreatic cancer has often spread to other parts of the body. Pancreatic cancer rarely occurs before the age of 40, and more than half of cases of pancreatic adenocarcinoma occur in those over 70. Risk factors for pancreatic cancer include tobacco smoking, obesity, diabetes, and certain rare genetic conditions. About 25% of cases are linked to smoking, and 5–10% are linked to inherited genes. Pancreatic cancer is usually diagnosed by a combination of medical imaging techniques such as ultrasound or computed tomography, blood tests, and examination of tissue samples (biopsy). The disease is divided into stages, from early (stage I) to late (stage IV). Screening the general population has not been found to be effective (Jemal and Bray, 2011; Cakir, *et al*, 2012).The risk of developing pancreatic cancer is lower among non-smokers, and people who maintain a healthy weight and limit their consumption of red or processed meat. A smoker's chance of developing the disease decreases if they stop smoking, and almost returns to that of the rest of the population after 20 years. Pancreatic cancer can be treated with surgery, radiotherapy, chemotherapy, palliative care, or a combination of these. Treatment options are partly based on the cancer stage. Surgery is the only treatment that can cure pancreatic adenocarcinoma, and may also be done to improve quality of life without the potential for cure. Pain management and medications to improve digestion are sometimes needed. Early palliative care is recommended even for those receiving treatment that aims for a cure (Jemal and Bray, 2011; Cakir, *et al*, 2012).

In 2015, pancreatic cancers of all types resulted in 411,600 deaths globally. Pancreatic cancer is the fifth most common cause of death from cancer in the United Kingdom, and the fourth most common in the United States. The disease occurs most often in the developed world, where about 70% of the new cases in 2012 originated. Pancreatic adenocarcinoma typically has a very poor prognosis: after diagnosis, 25% of people survive one year and 5% live for five years. For cancers diagnosed early, the five-year survival rate rises to about 20%. Neuroendocrine cancers have better outcomes; at five years from diagnosis, 65% of those diagnosed are living, though survival varies considerably depending on the type of tumor.

The many types of pancreatic cancer can be divided into two general groups. The vast majority of cases (about 95%) occur in the part of the pancreas which produces digestive enzymes, known as the exocrine component. There are several sub-types of exocrine pancreatic cancers, but their diagnosis and treatment have much in common. The small minority of cancers that arise in the hormone-producing (endocrine) tissue of the pancreas have different clinical characteristics and are called pancreatic neuroendocrine tumors, sometimes abbreviated as "PanNETs". Both groups occur mainly (but not exclusively) in people over 40, and are slightly more common in men, but some rare sub-types mainly occur in women or children. (Dubas and Ingraffea, 2013).

ABOUT THE PANCREAS AND IT'S CANCER

The pancreas is a pear-shaped gland located in the abdomen between the stomach and the spine. It is made up of 2 major components:

- The exocrine component is made up of ducts and small sacs called acini on the end of the ducts. This part of the pancreas makes specialized proteins called enzymes that are released into the small intestine to help the body digest and break down food, particularly fats.
- The endocrine component of the pancreas is made up of cells lumped together in different locations within this part of the pancreas, called islets of Langerhans. These cells make specific hormones, most importantly insulin. Insulin is the substance that helps control the amount of sugar in the blood. This portion of the pancreas also makes other hormones, such as glucagon, somatostatin, pancreatic polypeptide (PP), and vasoactive intestinal peptide (VIP). Each of these hormones plays an important role in regulating the body's metabolism (Anand, et al, 2008). *History of Pancreatic Cancer:*

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 histopathologic diagnosis was eventually recorded by the American clinician Jacob Mendes Da Costa, who also doubted the reliability of Morgagni's interpretations. By the start of the 20th century, cancer of the head of the pancreas had become a well-established diagnosis (Busnardo, et al, 1983).

In 1888, PanNETs received the recognition regarding the possibility of cancer of the islet cells. The first case of hyperinsulinism due to a tumor of this type was reported in 1927. Recognition of a non-insulin-secreting type of PanNET is generally ascribed to the American surgeons, R. M. Zollinger and E. H. Ellison, who gave their names to Zollinger–Ellison syndrome, after postulating the existence of a gastrin-secreting pancreatic tumor in a report of two cases of unusually severe peptic ulcers published in 1955. In 2010, the WHO recommended that PanNETs be referred to as "neuroendocrine" rather than "endocrine" tumors. The first reported partial pancreaticoduodenectomy was performed by the Italian surgeon Alessandro Codivilla in 1898, but the patient only survived 18 days before succumbing to complications. Early operations were compromised partly because of mistaken beliefs that people would die if their duodenum were removed, and also, at first, if the flow of pancreatic juices stopped. Later it was thought, also mistakenly, that the pancreatic duct could simply be tied up without serious adverse effects; in fact, it will very often leak later on. In 1907–08, after some more unsuccessful operations by other surgeons, experimental procedures were tried on corpses by French surgeons (Are, *et al*, 2011). In 1912 the German surgeon Walther Kausch was the first to remove large parts of the duodenum and pancreas together (en bloc). This was in Breslau, now Wrocław in Poland. 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 Oldfather 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 first operation was unplanned, as cancer was only discovered in the operating theater. Whipple's success showed the way for the future, but the operation remained a difficult and dangerous one until recent decades. He published several refinements to his procedure, including the first total removal of the duodenum in 1940, but he only performed a total of 37 operations (Are, *et al*, 2011).

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, but about 25% of people never left hospital alive as late as the 1970s (Cameron, *et al*, 2006). In the 1970s a group of American surgeons wrote urging that the procedure was too dangerous and should be abandoned. Since then outcomes in larger centers have improved considerably, and mortality from the operation is often less than 4%. In 2006 a report was published of a series of 1,000 consecutive pancreaticoduodenectomies performed by a single surgeon from Johns Hopkins Hospital between 1969 and 2003. The rate of these operations had increased steadily over this period, with only three of them before 1980, and the median operating time reduced from 8.8 hours in the 1970s to 5.5 hours in the 2000s, and mortality within 30 days or in hospital was only 1%. Another series of 2,050 operations at the Massachusetts General Hospital between 1941 and 2011 showed a similar picture of improvement (Fernandez-del Castilo, *et al*, 2012).

Exocrine cancers in Pancreas

The exocrine group is dominated by pancreatic adenocarcinoma (variations of this name may add "invasive" and "ductal"), which is by far the most common type, representing about 85% of all pancreatic cancers. Nearly all these start in the ducts of the pancreas, as pancreatic ductal adenocarcinoma (PDAC). This is despite the fact that the tissue from which it arises – 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. This cancer originates in the ducts that carry secretions (such as enzymes and bicarbonate) away from the pancreas. About 60–70% of adenocarcinomas occur in the head of the pancreas. The next most common type, acinar cell carcinoma of the pancreas, arises in the clusters of cells that produce these enzymes, and represents 5% of exocrine pancreas cancers. Like the 'functioning' endocrine cancers described below, acinar cell carcinomas may cause over-production of certain molecules, in this case digestive enzymes, which may cause symptoms such as skin rashes and joint pain. Cystadenocarcinomas account for 1% of pancreatic cancers, and they have a better prognosis than the other exocrine types. Pancreatoblastoma is a rare form, mostly occurring in childhood, and with a relatively good prognosis. Other exocrine cancers include adenosquamous carcinomas, signet ring cell carcinomas, hepatoid carcinomas, colloid carcinomas, undifferentiated carcinomas, and undifferentiated carcinomas with osteoclast-like giant cells. Solid pseudopapillary tumor is a rare low-grade neoplasm that mainly affects younger women, and generally has a very good prognosis (Ryan, *et al*, 2014). Pancreatic mucinous cystic neoplasms are a broad group of pancreas tumors that have varying malignant potential. They are being detected at a greatly increased rate as CT scans become more powerful and common, and discussion continues as how best to assess and treat them, given that many are benign (Ryan, *et al*, 2014).

Pancreatic Neuroendocrine Cancer

The small minority of tumors that arise elsewhere in the pancreas are mainly pancreatic neuroendocrine tumors (PanNETs). 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 all considered to be rare. Pan.NETs 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 the bloodstream, 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 and gastrinomas, 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, non-functioning PanNETs are often diagnosed only after the cancer has spread to other parts of the body (Burns and Edil, 2012).

As with other neuroendocrine tumors, the history of the terminology and classification of PanNETs is complex. PanNETs are sometimes called "islet cell cancers", even though it is now known that they do not actually arise from islet cells as previously thought.

SIGNS AND SYMPTOMS OF PANCREATIC CANCER

Since pancreatic cancer usually does not cause recognizable symptoms in its early stages, the disease is typically not diagnosed until it has spread beyond the pancreas itself. This is one of the main reasons for the 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).

Bearing in mind that the disease is rarely diagnosed before the age of 40, common symptoms of pancreatic adenocarcinoma occurring before diagnosis include:

- Pain in the upper abdomen 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. It may be slightly relieved by bending forward. In the UK, about half of new cases of pancreatic cancer are diagnosed following a visit to a hospital emergency department for pain or jaundice. In up to two-thirds of people abdominal pain is the main symptom, for 46% of the total accompanied by jaundice, with 13% having jaundice without pain. (*Bond-Smith, et al, 2012).*
- Jaundice, a yellow tint to the whites of the eyes or skin, with or without pain, and possibly in combination with darkened urine. This results when a cancer in the head of the pancreas obstructs the common bile duct as it runs through the pancreas.[30]
- Unexplained weight loss, either from loss of appetite, or loss of exocrine function resulting in poor digestion (*Bond-Smith, et al, 2012).*
- The tumor may compress neighboring organs, disrupting digestive processes 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.[11] Constipation is common (*Alberts and Goldberg, 2009).*
- At least 50% of people with pancreatic adenocarcinoma have diabetes at the time of diagnosis. While long-standing diabetes is a known risk factor for pancreatic cancer (see Risk factors), the cancer can itself cause diabetes, in which case recent onset of diabetes could be considered an early sign of the disease *(Pannala, et al,* 2009). People over 50 who develop diabetes have eight times the usual risk of developing pancreatic adenocarcinoma within three years, after which the relative risk declines.

Other Findings of Pancreatic Cancer

- Trousseau's syndrome, in which blood clots form spontaneously in the portal blood vessels, the deep veins of the extremities, or the superficial veins anywhere on the body, may be associated with pancreatic cancer, and is found in about 10% of cases.
- 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 brought on by the biology of the disease.

Other common manifestations of the disease include: weakness and tiring easily; dry mouth; sleep problems; and a palpable abdominal mass (Sperti, et al, 2014).

Spread of the Symptoms of Pancreatic Cancer

The spread of pancreatic cancer to other organs (metastasis) may also cause symptoms. Typically, pancreatic adenocarcinoma first spreads to nearby lymph nodes, and later to the liver or to the peritoneal cavity, large intestine or lungs. It is uncommon for it to spread to the bones or brain.

Cancers in the 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 on the pancreas in such cases, whether in hope of a cure or to alleviate symptoms (Bosetti, et al, 2012).

RISK FACTORS

Risk factors for pancreatic adenocarcinoma include age, sex, and ethnicity. The risk of developing pancreatic cancer increases with age. Most cases occur after age 65, while cases before age 40 are uncommon. The disease is slightly more common in men than women, and in the United States is over 1.5 times more common in African Americans, though incidence in Africa is low (Larsson and Wolk, 2012).

Cigarette smoking is the best-established avoidable risk factor for pancreatic cancer, approximately doubling risk among long-term smokers, the risk increasing with the number of cigarettes smoked and the years of smoking. The risk declines slowly after smoking cessation, taking some 20 years to return to almost that of non-smokers (*Bosetti, et al, 2012).* Obesity; a BMI greater than 35 increases relative risk by about half (Peters, *et al,* 2016).

Family history; 5–10% of pancreatic cancer cases have an inherited component, where people have a family history of pancreatic cancer. The risk escalates greatly if more than one first-degree relative had the disease, and more modestly if they developed it before the age of 50. Most of the genes involved have not been identified (Peters, *et al,* 2016).

Hereditary pancreatitis gives a greatly increased lifetime risk of pancreatic cancer of 30–40% to the age of seventy. Screening for early pancreatic cancer may be offered to individuals with hereditary

pancreatitis on a research basis. Some people may choose to have their pancreas surgically removed to prevent cancer developing in the future (Reznik, *et al*, 2014).

Pancreatic cancer has been associated with the following other rare hereditary syndromes: Peutz–Jeghers syndrome due to mutations in the STK11 tumor suppressor gene (very rare, but a very strong risk factor); dysplastic nevus syndrome (or familial atypical multiple mole and melanoma syndrome, FAMMM-PC) due to mutations in the CDKN2A tumor suppressor gene; autosomal recessive ataxia-telangiectasia and autosomal dominantly inherited mutations in the BRCA2 gene and PALB2 gene; hereditary non-polyposis colon cancer (Lynch syndrome); and familial adenomatous polyposis. PanNETs have been associated with multiple endocrine neoplasia type 1 (MEN1) and von Hippel Lindau syndromes (Greenhalf, *et al*, 2009).

Chronic pancreatitis appears to almost triple risk, and as with diabetes, new-onset pancreatitis may be a symptom of a tumor. The risk of pancreatic cancer in individuals with familial pancreatitis is particularly high. Diabetes mellitus is a risk factor for pancreatic cancer and (as noted in the Signs and symptoms section) new-onset diabetes may also be an early sign of the disease. People who have been diagnosed with Type 2 diabetes for longer than ten years may have a 50% increased risk, as compared with non-diabetics. Specific types of food (as distinct from obesity) have not been clearly shown to increase the risk of pancreatic cancer. Dietary factors for which there is some evidence of slightly increased risk include processed meat, red meat, and meat cooked at very high temperatures (e.g. by frying, broiling or barbecuing) (Delpu , *et al*, 2011 and Pericleous, *et al*, 2014). Drinking alcohol excessively is a major cause of chronic pancreatitis, which in turn predisposes to pancreatic cancer. However, considerable research has failed to firmly establish alcohol consumption as a direct risk factor for pancreatic cancer. Overall, the association is consistently weak and the majority of studies have found no association, with smoking a strong confounding factor. The evidence is stronger for a link with heavy drinking, of at least six drinks per day (Pericleous, *et al*, 2014).

PATHO-PHYSIOLOGY

The patho-physiological aspects of pancreatic cancer include: Precancer; Invasive Cancer and Neuro-Endocrine Tumors (PanNETs).

(A). PRECANCER

Exocrine cancers are thought to arise from several types of precancerous lesions within the pancreas. But these lesions do not always progress to cancer, and the increased numbers detected as a by-product of the increasing use of CT scans for other reasons are not all treated. Apart from pancreatic serous cystadenomas (SCNs), which are almost always benign, four types of precancerous lesion are recognized (Wolfgang, *et al*, 2013).

The first is pancreatic intraepithelial neoplasia. These lesions are microscopic abnormalities in the pancreas and are often found in autopsies of people with no diagnosed cancer. These lesions may progress from low to high grade and then to a tumor. More than 90% of cases at all grades carry a faulty KRAS gene, while in grades 2 and 3 damage to three further genes – CDKN2A (p16), p53 and SMAD4 – are increasingly often found (Vincent, *et al*, 2011).

A second type are the intraductal papillary mucinous neoplasms (IPMNs). These are macroscopic lesions, which are found in about 2% of all adults. This rate rises to ~10% by age 70. These lesions have about a 25% risk of developing into invasive cancer. They may have KRAS gene mutations (~40–65% of cases) and in the GNAS Gs alpha subunit and RNF43, affecting the Wnt signaling pathway. Even if removed surgically, there remains a considerably increased risk of pancreatic cancer developing subsequently (Bussom and Saif, 2010).

The third type, pancreatic mucinous cystic neoplasms (MCNs) mainly occur in women, and may remain benign or progress to cancer. If these lesions become large, cause symptoms, or have suspicious features, they can usually be successfully removed by surgery. A fourth type of cancer that arises in the pancreas is the intraductal tubulopapillary neoplasm. This type was recognised by the WHO in 2010 and constitutes about 1–3% of all pancreatic neoplasms. Mean age at diagnosis is 61 years (range 35–78 years). About 50% of these lesions become invasive. Diagnosis depends on histology as these lesions are very difficult to differentiate from other lesions on either clinical or radiological grounds (Shahrokni and Saif, 2013).

(B). INVASIVE CANCER

The genetic events found in ductal adenocarcinoma have been well characterized, and complete exome sequencing has been done for the common types of tumor. Four genes have each been found to be mutated in the majority of adenocarcinomas: KRAS (in 95% of cases), CDKN2A (also in 95%), TP53 (75%), and SMAD4 (55%). The last of these are especially associated with a poor prognosis. SWI/SNF mutations/deletions occur in about 10–15% of the adenocarcinomas. The genetic alterations in several other types of pancreatic cancer and precancerous lesions have also been researched. Transcriptomics analyses and mRNA sequencing for the common forms of pancreatic cancer have found that 75% of human genes are expressed in the tumors, with some 200 genes more specifically expressed in pancreatic cancer as compared to other tumor types (Rooney and Shi, 2016).

(C). PANCREATIC NEUROENDOCRINE TUMORS (PanNETs)

The genes often found mutated in PanNETs are different from those in exocrine pancreatic cancer. For example, KRAS mutation is normally absent. Instead, hereditary MEN1 gene mutations give rise to MEN1 syndrome, in which primary tumors occur in two or more endocrine glands. About 40–70% of people born with a MEN1 mutation eventually develop a PanNet. Other genes that are frequently mutated include DAXX, mTOR and ATRX (Lewis and Yao, 2014).

DIAGNOSIS OF PANCREATIC CANCER

The symptoms of pancreatic adenocarcinoma do not usually appear in the disease's early stages, and are individually not distinctive to the disease. The symptoms at diagnosis vary according to the location of the cancer in the pancreas, which anatomists divide (from left to right on most diagrams) into the thick head, the neck, and the tapering body, ending in the tail.

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 will have had nausea, vomiting or a 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 (Thakker, *et al*, 2012).

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 (thrombophlebitis) known as Trousseau sign, or a previous attack of pancreatitis. A doctor may suspect pancreatic cancer when the onset of diabetes in someone over 50 years old is accompanied by typical symptoms such as unexplained weight loss, persistent abdominal or back pain, indigestion, vomiting, or fatty feces. Jaundice accompanied by a painlessly swollen gallbladder (known as Courvoisier's sign) may also raise suspicion, and can help differentiate pancreatic cancer from gallstones (Fitzgerald, et al, 2009).

Medical imaging techniques, such as computed tomography (CT scan) and endoscopic ultrasound (EUS) are used both to confirm the diagnosis and to help decide whether the tumor can be surgically removed (its "resectability"). On contrast CT scan, pancreatic cancer typically shows a gradually increasing radiocontrast uptake, rather than a fast washout as seen in a normal pancreas or a delayed washout as seen in chronic pancreatitis. Magnetic resonance imaging and positron emission tomography may also be used, and magnetic resonance cholangiopancreatography may be useful in some cases. 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). It may be used for a quick and cheap first examination before other techniques (Cyrus Piraka, *et al*, 2011 and Seufferlein, *et al*, 2012).

A biopsy by fine needle aspiration, often guided by endoscopic ultrasound, may be used where there is uncertainty over the diagnosis, but a histologic diagnosis is not usually required for removal of the tumor by surgery to go ahead (Cascinu, *et al*, 2010).

Liver function tests can show a combination of results indicative of bile duct obstruction (raised conjugated bilirubin, γ-glutamyl transpeptidase and alkaline phosphatase levels). CA19-9 (carbohydrate antigen 19.9) is a tumor marker that is frequently elevated in pancreatic cancer. However, it lacks sensitivity and specificity, not least because 5% of people lack the Lewis (a) antigen and cannot produce CA19-9. It has a sensitivity of 80% and specificity of 73% in detecting pancreatic adenocarcinoma, and is used for following known cases rather than diagnosis (Zyromski, *et al*, 2010).

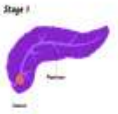
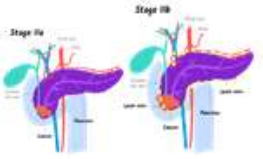
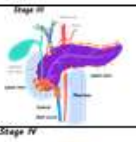
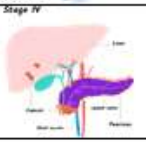
The most common form of pancreatic cancer (adenocarcinoma) is typically characterized by moderately to poorly differentiated glandular structures on microscopic examination. There is typically considerable desmoplasia or formation of a dense fibrous stroma or structural tissue consisting of a range of cell types (including myofibroblasts, macrophages, lymphocytes and mast cells) and deposited material (such as type I collagen and hyaluronic acid). This creates a tumor microenvironment that is short of blood vessels (hypovascular) and so of oxygen (tumor hypoxia). It is thought that this prevents many chemotherapy drugs from reaching the tumor, as one factor making the cancer especially hard to treat (He and Yuan, 2014; Okano and Suzuki, 2014).

STAGING IN PANCREATIC CANCER

Cancer staging is the process of determining the extent to which a cancer has developed by growing and spreading. Contemporary practice is to assign a number from I to IV to a cancer, with I being an isolated cancer and IV being a cancer which has spread to the limit of what the assessment measures. The stage generally takes into account the size of a tumor, whether it has invaded adjacent organs, how many

regional (nearby) lymph nodes it has spread to (if any), and whether it has appeared in more distant locations (metastasized). Cancer staging can be divided into a clinical stage and a pathologic stage. In the TNM (Tumor, Node, Metastasis) system, clinical stage and pathologic stage are denoted by a small "c" or "p" before the stage (e.g., cT3N1M0 or pT2N0). This staging system is used for most forms of cancer, except brain tumors and hematological malignancies. Clinical stage is based on all of the available information obtained before a surgery to remove the tumor. This stage may include information about the tumor obtained by physical examination, blood tests, radiologic examination, biopsy, and endoscopy. Pathologic stage adds additional information gained by examination of the tumor microscopically by a pathologist after it has been surgically removed. Because they use different criteria, clinical stage and pathologic stage often differ. Pathologic staging is usually considered to be more accurate because it allows direct examination of the tumor in its entirety, contrasted with clinical staging which is limited by the fact that the information is obtained by making indirect observations of a tumor which is still in the body. However, clinical staging and pathologic staging often complement each other. Not every tumor is treated surgically, so pathologic staging is not always available. Also, sometimes surgery is preceded by other treatments such as

Table-1: Infography of staging in Pancreatic Cancer.

Serial No.	Pancreatic Cancer Stage	Infograph
1.	Stage – I: Stage-I.A: The tumor in the pancreas is 2 cm or smaller and has not spread to lymph nodes or other parts of the body. Stage-I.B:The tumor in the pancreas is larger than 2 cm and has not spread to lymph nodes or other parts of the body.	
2.	Stage-II.A: The tumor extends beyond the pancreas but has not spread to nearby lymph nodes, major blood vessels, or other parts of the body. **Stage-II.B:** The tumor is any size and is either limited to or extends beyond the pancreas and has spread to lymph nodes but not to major blood vessels or other parts of the body. Stage I and II cancers that have not spread beyond the pancreas may be resectable, or able to be surgically removed.	
3.	Stage-III: The tumor has spread to nearby blood vessels, may or may not have spread to nearby lymph nodes, but the cancer has not spread to other parts of the body. Cancer in this stage is considered to be locally advanced.	
4.	Stage-IV: The cancer has spread to other parts of the body. This is called metastatic cancer.	

chemotherapy and radiation therapy which shrink the tumor, so the pathologic stage may underestimate the true stage (https://www.cancer.org/cancer/pancreatic-cancer/detection-diagnosis-staging/staging.html). Pancreatic cancer is usually staged following a CT scan. 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 (UICC). The AJCC-UICC staging system designates four main overall stages, ranging from early to advanced disease, based on TNM classification of Tumor size, spread to lymph **N**odes, and **M**etastasis (Stoita, *et al*, 2011).

To help decide treatment, the tumors are also divided into three broader categories based on whether surgical removal seems possible: in this way, tumors are judged to be "resectable", "borderline resectable", or "unresectable" (Gurusamy, *et al*, 2014). When the disease is still in an early stage (AJCC-UICC stages I and II), without spread to large blood vessels or distant organs such as the liver or lungs, surgical resection of the tumor can normally be performed, if the patient is willing to undergo this major operation and is thought to be sufficiently fit. The AJCC-UICC staging system allows distinction between stage III tumors that are judged to be "borderline resectable" (where surgery is technically feasible because the celiac axis and superior mesenteric artery are still free) and those that are "unresectable" (due to more locally advanced disease); in terms of the more detailed TNM classification, these two groups correspond to T3 and T4 respectively. Locally advanced adenocarcinomas have spread into neighboring organs, which may be any of the following (in roughly decreasing order of frequency): the duodenum, stomach, transverse colon, spleen, adrenal gland, or kidney. Very often they also spread to the important blood or lymphatic vessels and nerves that run close to the pancreas, making surgery far more difficult. Typical sites for metastatic spread (stage IV disease) are the liver, peritoneal cavity and lungs, all of which occur in 50% or more of fully advanced cases (Mollberg, *et al*, 2011). Staging cancer is a standardized way to classify a tumor based on its size, whether it has spread, and where it has spread. In other words, staging measures the extent of the disease. Knowing the stage of cancer helps doctors determine which treatment options are the best approach (https://letswinpc.org/stages/).

PREVENTION AND SCREENING

Apart from not smoking, the American Cancer Society recommends keeping a healthy weight, and increasing consumption of fruits, 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. 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 possibly a beneficial effect from whole grains, folate, selenium, and non-fried fish. In the general population, screening of large groups is not currently considered effective, although newer techniques, and the screening of tightly targeted groups, are being evaluated. Nevertheless, regular screening with endoscopic ultrasound and MRI/CT imaging is recommended for those at high risk from inherited genetics (Alamo, *et al*, 2014).

MANAGEMENT

Cancer and its treatments are well-recognized risk factors for venous thromboembolism (VTE). Although the incidence of VTE in cancer patients is not well documented, there is evidence that the absolute risk depends on the tumor type, the stage or extent of the cancer, and treatment with antineoplastic agents. The most common cancer types seen in patients with thrombosis are breast, colorectal and lung, reflecting the prevalence of these malignancies in the general population. When the underlying prevalence is taken into account, cancers of the pancreas, ovary and brain are the most strongly associated with thrombotic

complications. Although idiopathic thrombosis can be the first manifestation of an occult malignancy, extensive screening for cancer in these patients has not been shown to improve survival and is not warranted. Despite treatment, cancer patients with thrombosis have a poor prognosis. This is likely due to premature deaths from recurrent VTE and to the aggressive nature of the underlying cancer. Further research is needed to address the many clinical questions in the management of thrombosis in patients with cancer (Muhammad Adnan Sohail and Muhammad Wasif Saif, 2009).

A key assessment that is made after diagnosis 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. The exact location of the tumor is also a significant factor, and CT can show how it relates to the major blood vessels passing close to the pancreas. The general health of the person must also be assessed, though age in itself is not an obstacle to surgery. Chemotherapy and, to a lesser extent, radiotherapy are likely to be offered to most people, whether or not surgery is possible. Specialists advise that the management of pancreatic cancer should be in the hands of a multidisciplinary team including specialists in several aspects of oncology, and is, therefore, best conducted in larger centers (Wolfgang, *et al*, 2013).

SURGERY FOR PANCREATIC CANCER

Surgery with the intention of a cure is only possible in around one-fifth (20%) of new cases. Although CT scans help, in practice it can be difficult to determine whether the tumor can be fully removed (its "resectability"), and it may only become apparent during surgery that it is not possible to successfully remove the tumor without damaging other vital tissues. Whether or not surgical resection can be offered depends on various factors, including the precise extent of local anatomical adjacency to, or involvement of, the venous or arterial blood vessels, as well as surgical expertise and a careful consideration of projected post-operative recovery. The age of the person is not in itself a reason not to operate, but their general performance status needs to be adequate for a major operation (Mollberg, *et al*, 2011; Gurusamy, *et al*, 2014).

One particular feature that is evaluated is the encouraging presence, or discouraging absence, of a clear layer or plane of fat creating a barrier between the tumor and the vessels. Traditionally, an assessment is made of the tumor's proximity to major venous or arterial vessels, in terms of "abutment" (defined as the tumor touching no more than half a blood vessel's circumference without any fat to separate it), "encasement" (when the tumor encloses most of the vessel's circumference), or full vessel involvement. A resection that includes encased sections of blood vessels may be possible in some cases, particularly if preliminary neoadjuvant therapy is feasible, using chemotherapy and/or radiotherapy (Lopez, *et al*, 2014).

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 (this will always be done), indicating the cancer has not been entirely removed. Furthermore, cancer stem cells are usually not evident microscopically, and if they are present they may continue to develop and spread. An exploratory laparoscopy (a small, camera-guided surgical procedure) may therefore be performed to gain a clearer idea of the outcome of a full operation (Polistina, *et al*, 2014).

For cancers involving the head of the pancreas, the Whipple procedure is the most commonly attempted curative surgical treatment. This is a major operation which involves removing the pancreatic head and

the curve of the duodenum together ("pancreato-duodenectomy"), making a bypass for food from the stomach to the jejunum ("gastro-jejunostomy") and attaching a loop of jejunum to the cystic duct to drain bile ("cholecysto-jejunostomy"). It can be performed only if the person is likely to survive major surgery and if the cancer is localized without invading local structures or metastasizing. It can, therefore, be performed only in a minority of cases. Cancers of the tail of the pancreas can be resected using a procedure known as a distal pancreatectomy, which often also entails removal of the spleen. Nowadays, this can often be done using minimally invasive surgery (Gillen, *et al*, 2010).

Although curative surgery no longer entails the very high death rates that occurred until the 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 complication of surgery is difficulty in emptying the stomach. Certain more limited surgical procedures may also be used to ease symptoms for instance, if the cancer is invading or compressing the duodenum or colon. In such cases, bypass surgery might overcome the obstruction and improve quality of life but is not intended as a cure (Christians and Evans, 2014).

CHEMOTHERAPY FOR PANCREATIC CANCER

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. In people not suitable for curative surgery, chemotherapy may be used to extend life or improve its quality. Before surgery, neoadjuvant chemotherapy or chemoradiotherapy may be used in cases that are considered to be "borderline resectable" in order to reduce the cancer to a level where surgery could be beneficial. In other cases neoadjuvant therapy remains controversial, because it delays surgery (Tsvetkova and Asmis, 2014).Gemcitabine was approved by the United States Food and Drug Administration (FDA) in 1997, after a clinical trial reported improvements in quality of life and a 5-week improvement in median survival duration in people with advanced pancreatic cancer. This was the first chemotherapy drug approved by the FDA primarily for a nonsurvival clinical trial endpoint. Chemotherapy using gemcitabine alone was the standard for about a decade, as a number of trials testing it in combination with other drugs failed to demonstrate significantly better outcomes. However, the combination of gemcitabine with erlotinib was found to increase survival modestly, and erlotinib was licensed by the FDA for use in pancreatic cancer in 2005 (Zhan, *et al*, 2015).

The FOLFIRINOX chemotherapy regimen using four drugs was found more effective than gemcitabine, but with substantial side effects, and is thus only suitable for people with good performance status. This is also true of protein-bound paclitaxel (nab-paclitaxel), which was licensed by the FDA in 2013 for use with gemcitabine in pancreas cancer. By the end of 2013, both FOLFIRINOX and nab-paclitaxel with gemcitabine were regarded as good choices for those able to tolerate the side-effects, and gemcitabine remained an effective option for those who were not. A head-to-head trial between the two new options is awaited, and trials investigating other variations continue. However, the changes of the last few years have only increased survival times by a few months. Clinical trials are often conducted for novel adjuvant therapies (Heinemann, *et al*, 2013; Tsvetkova and Asmis, 2014; Tanase, *et al*, 2015; Allen, *et al*, 2016).

RADIOTHERAPY FOR PANCREATIC CANCER

The role of radiotherapy as an auxiliary (adjuvant) treatment after potentially curative surgery has been controversial since the 1980s. The European Society for Medical Oncology recommends that adjuvant radiotherapy should only be used for people enrolled in clinical trials. However, there is a continuing

tendency for clinicians in the US to be more ready to use adjuvant radiotherapy than those in Europe. Many clinical trials have tested a variety of treatment combinations since the 1980s, but have failed to settle the matter conclusively.

Radiotherapy may form part of treatment to attempt to shrink a tumor to a resectable state, but its use on unresectable 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 tumors (Thota, *et al*, 2014).

Radiation therapy is occasionally used if there is pain due to anatomic extension, such as metastasis to bone. Some PanNETs absorb specific peptides or hormones, and these PanNETs may respond to nuclear medicine therapy with radiolabeled peptides or hormones such as iobenguane (iodine-131-MIBG). Radiofrequency ablation (RFA), cryoablation, and hepatic artery embolization may also be used (Bodei, *et al*, 2014).

PALLIATIVE CARE FOR PANCREATIC CANCER

Palliative care is medical care which focuses on treatment of symptoms from serious illness, such as cancer, and improving quality of life. Because pancreatic adenocarcinoma is usually diagnosed after it has progressed to an advanced stage, palliative care as a treatment of symptoms is often the only treatment possible (Buanes, 2014).

Palliative care focuses not on treating the underlying cancer, but on treating symptoms such as pain or nausea, and can assist in decision-making, including when or if hospice care will be beneficial. Pain can be managed with medications such as opioids or through procedural intervention, by a nerve block on the celiac plexus (CPB). This alters or, depending on the technique used, destroys the nerves that transmit pain from the abdomen. CPB is a safe and effective way to reduce the pain, which generally reduces the need to use opioid painkillers, which have significant negative side effects (Arcidiacono, *et al*, 2011).

Other symptoms or complications that can be treated with palliative surgery are obstruction by the tumor of the intestines or bile ducts. For the latter, which occurs in well over half of cases, a small metal tube called a stent may be inserted by endoscope to keep the ducts draining. Palliative care can also help treat depression that often comes with the diagnosis of pancreatic cancer.

Both surgery and advanced inoperable tumors often lead to digestive system disorders from a lack of the exocrine products of the pancreas (exocrine insufficiency). These can be treated by taking pancreatin which contains manufactured pancreatic enzymes, and is best taken with food. Difficulty in emptying the stomach (delayed gastric emptying) is common and can be a serious problem, involving hospitalization. Treatment may involve a variety of approaches, including draining the stomach by nasogastric aspiration and drugs called proton-pump inhibitors or H2 antagonists, which both reduce production of gastric acid. Medications like metoclopramide can also be used to clear stomach contents (Jemal, *et al*, 2007; Lozano, *et al*, 2012).

FOLFIRINOX for Pancreatic Cancer

A recent study published in the New England Journal of Medicine, a leading medical journal, adds hope. The drug gemcitabine is considered the standard treatment. The study looked at 342 patients with pancreatic cancer. A combination drug treatment that consisted of oxaliplatin, irinotecan, fluorouracil and leucovorin (FOLFIRINOX) was tried on half of the patients. The other group took gemcitabine. Patients in both groups underwent six months of chemotherapy. FOLFIRINOX was found to be associated with a survival advantage. The median survival rate was 11.1 months in the FOLFIRINOX group compared to 6.8 months in the gemcitabine group. It was also noticed that the median progression-free survival was 6.4 months in the FOLFIRINOX group compared to 3.3 months in the gemcitabine group.

The result is of great significance. A diagnosis of pancreatic cancer was often taken equivalent to a death sentence. A more conclusive study that would confirm the findings would mean a change in the mentioned scenario.

FOLFIRINOX is a chemotherapy regimen for treatment of advanced pancreatic cancer. It is made up of the following four drugs:

- FOL – folinic acid (leucovorin), a vitamin B derivative that modulates/potentiates/reduces the side effects of fluorouracil;
- F – fluorouracil (5-FU), a pyrimidine analog and antimetabolite which incorporates into the DNA molecule and stops DNA synthesis;
- IRIN – irinotecan (Camptosar), a topoisomerase inhibitor, which prevents DNA from uncoiling and duplicating; and
- OX – oxaliplatin (Eloxatin), a platinum-based antineoplastic agent, which inhibits DNA repair and/or DNA synthesis.

The regimen emerged in 2010 as a new treatment for patients with metastatic pancreatic cancer. (Conroy, *et al*, 2013; Faris, *et al*, 2013). A 2011 study published in the New England Journal of Medicine found that FOLFIRINOX produced the longest improvement in survival ever seen in a phase III clinical trial of patients with advanced pancreatic cancer, with patients on the FOLFIRINOX treatment living approximately four months longer than patients receiving the standard gemcitabine treatment (11.1 months compared with 6.8 months) (Conroy, *et al*, 2011). However, FOLFIRINOX is a potentially highly toxic combination of drugs with serious side effects, and only patients with good performance status are candidates for the regimen (Thota, *et al*, 2014).

In 2013, the U.S. Food and Drug Administration approved protein-bound paclitaxel (also known as nab-paclitaxel, sold as Abraxane) used with gemcitabine. This regimen may be less toxic—but perhaps less effective—alternative to FOLFIRINOX for treating late-stage pancreatic cancer. Differences in the trials, and the lack of a direct trial comparing the two regimens, preclude a final conclusion (Thota, *et al*, 2014).

In the United Kingdom, the National Institute for Health and Care Excellence (NICE), in a draft guidance issued in 2014, rejected that treatment due to concerns of side effects, efficacy, and cost relative to Gemzar (gemcitabine). However, on the 18th of May 2017 NICE issued a reappraisal for the use of Abraxane in the UK. This was in response to Celgene putting forward a Patient Access Scheme (PAS) proposal, which would bring down the cost of the drug. Pancreatic adenocarcinoma and the other less

common exocrine cancers have a very poor prognosis, as they are normally diagnosed at a late stage when the cancer is already locally advanced or has spread to other parts of the body. Outcomes are 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% although the outlook varies considerably according to the type.

CONCLUSION

Worldwide efforts on many levels are underway to understand pancreatic cancer, but progress has been slow, particularly into understanding the disease's causes. There are several fundamental unanswered questions. The nature of the changes that lead to the disease are being intensely investigated, such as the roles played by genes such as KRAS and p53. A key question is the timing of events as the disease develops and progresses – particularly the role of diabetes, and how and when the disease spreads.

Research on early detection is ongoing. For instance, the European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) trial is aiming to determine whether regular screening is appropriate for people with a family history of the disease, or who have hereditary pancreatitis. The knowledge that new onset of diabetes can be an early sign of the disease could facilitate timely diagnosis and prevention if a workable screening strategy can be developed.

ACKNOWLEDGEMENT

Expertise support from International Academic Journals and Agricultural Development Trust, Baramati India deserve appreciations and exert a grand salutary influence. The Science Culture of Someshwar Science College, Someshwarnagar Tal. Baramati Dist. Pune (India) served a lot to orchestrate the progression of analysis of results and finalize the manuscript.

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