Acta Scientific ANATOMY

Volume 2 Issue 5 August 2023

Review Article

Cancer of the Deadliest: Pancreatic Cancer!

Dhananjay Kumar[1], V Shanmukha Varalakshmi[2]* and Aleeza Muneer[3]

[1]Associate Professor, Department of Anatomy, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, U.P, India

[2]Associate Professor, Department of Anatomy, Rohilkhand Medical College and Hospital, Bareilly, UP, India

[3]Tutor, Department of Anatomy, Rohilkhand Medical College and Hospital, Bareilly, U.P, India

***Corresponding Author:** V Shanmukha Varalakshmi, Associate Professor, Department of Anatomy, Rajshree Medical Research Institute, India.

Received: August 10, 2023

Published: August 29, 2023

© All rights are reserved by **V Shanmukha Varalakshmi., *et al.***

Abstract

Pancreatic cancer is always difficult to diagnose in early stages and results in high mortality. Pancreas is a deep seated mixed variety of gland having exocrine and endocrine parts. Over 90% of all pancreatic tumours is exocrine in nature. Rest 10% are noticed in endocrine pancreas and are termed as neuroendocrine tumours. Pancreatic ductal adenocarcinoma has the lowest five-year relative survival rate compared to all other solid tumour malignancies and is expected to become the second-leading cause of cancer-related death in the United States by 2030. Even though there are relative advancements in diagnostic tools management of pancreatic cancer is becoming a challenging tsk where only about 4% of patients are expected to survive 5 years after diagnosis. Genetic, racial and hereditary factors are associated with this disease condition. Old age and male gender are more susceptible for its occurrence. Smoking, alcohol consumption are also causative factors for pancreatic cancer. Awareness about the types and stages of pancreatic cancer with the hidden causative factors is the need of the hour.

Keywords: Pancreatic Ductal Adeno Carcinoma; Islets of Langerhans; Neuroendocrine Tumour

Introduction

According to the Global cancer statistics, 2020, Pancreatic Cancer is 12th most common cancers worldwide. It is 11th most common cancers in India [1].

However, the age associated incidence rate of pancreatic cancer in India is lowest in the world [2]. Pancreatic cancer prevalence is more in the urban male population of western and northern parts of India [3]. World Pancreatic cancer day is observed on 15th November.

28,000 new cases of Pancreatic cancer occur in United States every year [4]. It is the fourth leading cause of cancer related death for both men and women in the United States only next to lung, colon and breast [5,6]. It is one of the most lethal cancers with 100% mortality rate. Despite of developments in detection and management of pancreatic cancer, only about 4% of patients will live 5 years after diagnosis [7]. Overall, average five-year survival rate is 6% differing very little between developed and developing countries [8]. Expected survival in non-operative cases is one year whereas, about five years survival was noted in operative cases [9]. Around half of the patients with pancreatic cancer approach a general physician with symptoms felt for more than one month. This proportion reached 70% in the presence of jaundice whereas other symptoms were rarely recognized early in the general population.

Seventy percent of pancreatic cancers are located in the head of the pancreas, and obstructive jaundice is often the first symptom leading to diagnosis, whereas pain or other symptoms such as asthenia, loss of weight or anorexia, may have a more insidious onset [10]. It is poorly diagnosed compared to other digestive tract cancers, because of its location.

Anatomy of pancreas

Pancreas develops during fourth to seventh weeks of intrauterine life. Major part of pancreas develops from dorsal out pouching of endodermal lining of duodenum into dorsal meso-gastrium. It gives rise to superior part of head, neck, body and tail. Distal to the former and close to the bile duct a ventral out pouching arises from the duodenal wall into ventral meso-gastrium. It gives rise to posterior part of head and uncinate process. Due to axial rotation of duodenum, both dorsal and ventral pancreatic buds approximate and fuse with each other [11]. Simultaneously, there is a fusion of meso-duodenum with posterior abdominal wall called fusion fascia or meso-pancreas. The fusion fascia of the head of the pancreas is called the "fusion fascia of Treitz" and that of the body and tail of the pancreas is termed the "fusion fascia of Toldt" [12]. This is closely related to pancreaticoduodenal arcades of arteries, veins and nerves. It also covers the extra pancreatic nerve plexus, superior mesenteric artery and portal vein. In the third month of foetal life, islets develop in the parenchymatous tissue of pancreas [13].

The main pancreatic duct is formed by distal part of dorsal pancreatic duct and the entire ventral pancreatic duct. The proximal part of dorsal pancreatic duct either obliterates or persists as accessory pancreatic duct.

Pancreas has head, uncinate process, neck, body and tail. It is situated in the posterior abdominal wall with an upward inclination. It rests successively over second lumbar vertebra, first lumbar vertebra and twelfth thoracic vertebra extending from right to left. Head is situated in the C-shaped concavity of duodenum, separated by superior and inferior pancreaticoduodenal vessels. Uncinate process is a small triangular extension from the inferior part of head to the left. It is more in posterior plane compared to rest of the gland. It is sandwiched between superior mesenteric vessels in front and abdominal aorta behind. During pancreatitis, the common pathological inflammation of pancreas, secondary inflammations are noticed in adjacent vessels. Inflammatory aneurysm of superior mesenteric vessels causes hemorrhage. Thrombosis of superior mesenteric vein leads to lethal venous ischemia of the small intestine. Neck is the constricted part between head and body. Posteriorly, it is in close association with the portal vein. Body is prismoid in cross section with splenic artery running along superior border and splenic vein along its posterior surface. It separated from stomach and spleen by lesser sac. In acute pancreatitis fluid accumulates in the lesser sac forming pseudo pancreatic cysts. Tail extends into the hilum of pancreas lodging in lienorenal ligament. The union of many smaller ducts within the body forms the main pancreatic duct, duct of Wirsung. The duct runs from left to right and pierces the duodenal wall. It unites with bile duct to form ampulla of Vater. The later opens at the summit of major duodenal papilla. The secretion from uncinate process enters into the accessory pancreatic duct, the duct of Santorini. It crosses anterior to the main pancreatic duct and opens on minor duodenal papilla.

Profuse arterial and venous supply to the pancreas and closely related blood vessels makes the resection of pancreas quite difficult task. Lymphatic vessels of this organ drain mostly in pancreatico-splenic lymph nodes, few into pancreatico-duodenal lymph nodes and others into superior mesenteric pre-aortic lymph nodes. The lymph nodes with a high metastatic rate were those along the splenic artery (50%), the inferior body lymph nodes (35%), lymph nodes around the common hepatic artery (25%), and the paraaortic lymph nodes (20%) [14].

All these lymph nodes are closely associated with the nerve plexus. Extrapancreatic neural plexus is divided into two main sections. The first portion of the plexus pancreaticus capitalis extends from the right celiac ganglion to the upper medial margin of the uncinate process of the pancreas. The second portion of the plexus pancreaticus capitalis extends from the superior mesenteric artery to the medial margin of the uncinate process [15]. Patients with carcinoma of the head of the pancreas shows the involvement of the second portion of the plexus pancreaticus capitalis. In patients with carcinoma of the body and tail of the pancreas, splenic plexus was the most frequent site of invasion. This neuronal involvement is one of the reasons for difficult surgical resection and recurrence of pancreatic cancer [14].

Types of pancreatic cancer

Pancreas is a mixed gland having both endocrine component for hormone production and exocrine component for the production of digestive enzymes. Endocrine component comprising Islets of Langerhans is rarely involved with cancer compared to exocrine part. These tumors are often called islet cell tumors or neuroen-

docrine tumors. The exocrine pancreas is most frequently affected. It is the ductal part of exocrine pancreas involved and hence is commonly called Pancreatic ductal adenocarcinoma (PDAC) or Pancreatic cancer. Several other exocrine types of cancer are cystic tumors, acinar cell carcinomas, ampullary cancer, intraductal papillary mucinous neoplasms (IPMNs).

Other varieties include lymphoma, sarcoma, pancreato blastoma and pseudopapillary neoplasms. If the cancer is associated with exocrine part, it can lead to mal absorption of nutrients. If it is related to endocrine part, it can cause over production of certain hormones and lead to endocrine related syndromes.

Causative factors

- **Genetic factors:** Inherited and acquired mutations of specific cancer genes cause pancreatic cancer. Different types of pancreatic cancers are due to identified 63 genetic alterations. An oncogene KRAS and tumor suppressor genes like TP53, p16/CDKN2A and SMAD4 are few genes that commonly undergo point mutations and cause pancreatic cancer. There are certain gene alterations occur at germline level like BRCA2 (hereditary breast and ovarian cancer syndrome), PALB2 (Partner and Localizer of BRCA2), p16 (familial melanoma), PRSS1 (familial pancreatitis) and NF1 (neurofibromatosis, type 1) that cause familial pancreatic cancer [16]. Other inherited syndromes that may be linked to pancreatic cancer include: Lynch Syndrome, Peutz-Jeghers Syndrome (PJS), Von Hippel-Lindau Syndrome (VHL), MEN1 (multiple endocrine neoplasia type 1) syndrome: A rare genetic disorder that may be a risk factor for malignant islet cell tumors.
- **Racial factors:** Pancreatic cancer exhibits racial differences at the molecular level. Survival rate of Asian patients is higher than non-Asians. Race related genetic factors or differences in environmental exposure that determine survival. Developed countries like North America and Europe are more prone to pancreatic cancer. Asian patients were found to have less aggressive tumors than either white or black patients did [17].
- **Hereditary pancreatitis:** Existing data reveals greater strength of association between chronic pancreatitis and pancreatic cancer. Hereditary and tropical pancreatitis are more likely to end up in malignancy. High risk in these patients may be due to the early onset of pancreatitis, so that over prolonged time there is progression of disease, tissue destruction and development of defects in cellular repair [18]. In India 4% of chronic pancreatitis were noted with pancreatic cancer [19,20].
- **Smoking:** Smoking is one of the prime factors for pancreatic cancer. Risk of pancreatic cancer positively increases with the lifetime cigarette consumption. It causes about 75% increase chances of pancreatic cancer. Direct intake of tobacco was also noted to have similar effect. It was the only modifiable risk factor where levels fall for ex-smokers after 10-15 years of quitting smoking equivalent to that of non smokers [21]. In countries like USA the pancreatic cancer rates declined significantly in white males with a curb on cigarette smoking. Tobacco carcinogens reach pancreas mostly through blood stream. There is also possibility for these carcinogens to invade pancreas by exposure to bile. This route is prone for cancers in head region of this organ. Cigarette smoking is however considered as a serious risk factor compared to pipe and cigar smoking but the results need further investigation [22].
- **Age:** Pancreatic cancer is commonly a old age cancer noticed in adults greater than 60 years of age. Only 5-10% of the cases were noted before the age of 50 years
- **Sex:** Males are 1.5 to 2 times more commonly effected than females [23].
- **BMI:** Increased BMI in early adulthood is strongly associated risk factor. It has more impact than those with subsequent increase in BMI. Recent studies revealed Obesity has a severe impact on overall survival rate in patients with pancreatic cancer. This effect of BMI was stronger among patients with tumor resection than among those with unresected tumors. Obesity at an older age or shortly before the cancer diagnosis was associated with a reduced overall survival time. Weight control at younger ages should be one of the primary strategies to prevent pancreatic cancer [5].

Stages of pancreatic cancer

- **Nodular:** Tumor appears in the form of small nodules within the pancreas. These nodules are resectable.
- **Borderline:** It is difficult to remove this tumor surgically. With the help of initial chemotherapy treatment, the margins of the tumor are cured. When the negative margin free of visible tumor cells forms then the tumor mass is resected.

- **Locally advanced:** it is defined as locally advanced when vascular extension reaches the coeliac trunk, the superior mesenteric artery, or the portomesentric venous junction (obstruction), or in the event of lymph node invasion reaching the 2nd or 3rd nodal relay [24].
- **Metastatic:** In this stage the tumor has spread beyond the area of pancreas into organs such as liver, lung and other distant organs of abdomen. It is the end stage of neoplastic progression of pancreatic neoplasia. It takes more than a decade for the metastatic spread from the initial phase of mutation. It suggests that early detection of pancreatic neoplasia is beneficial and possible life saving measure [25].

Conclusion

Even though knowledge in preoperative diagnosis, surgical techniques and postoperative care increased drastically, it could not improve the survival rates of pancreatic cancer patients. Lack of early symptoms renders a poor diagnosis of this disease with surgery being main treatment modality.

Bibliography

1. Pancreatic cancer statistics (2018).
2. Parkin DM., *et al.* "Cancer incidence in five continents". *International Agency for Research on Cancer* (1997): 7.
3. Makrocare (2018).
4. Kulke MH. "Metastatic pancreatic cancer". *Current Treatment Options in Oncology* 3.6 (2002):449-457.
5. Li D., *et al.* "BodyMass Index and Risk, Age of onset, and survival in patients with pancreatic cancer". *JAMA* 301.24 (2009):2553-2562.
6. Sellam F., *et al.* "Delayed diagnosis of pancreatic cancer reported as more common in a population of North African young adults". *Journal of Gastrointestinal Oncology* 6.5 (2015):505-510.
7. Vincet A., *et al.* "*The Lancet* 378.9791 (2011):607-20.
8. Ilic M and Ilic I. "Epidemiology of pancreatic cancer". *World Journal of Gastroenterology* 22.44 (2016): 9694-9705.
9. Campbell PJ., *et al.* "The patterns and dynamics of genomic instability in metastatic pancreatic cancer". *Nature* 467 (2010):1109-1113.
10. Jooste V., *et al.* "Pancreatic cancer: Wait times from presentation to treatment and survival in a population-based study". *International Journal of Cancer* 139.5 (2016):1073-1080.
11. Borghi F., *et al.* "Embryologic bases of extended radical resection in pancreatic cancer". *The Archives of Surgery* 133 (1998): 297-301.
12. Kimura W. "Surgical anatomy of the pancreas for limited resection". *Journal of Hepato-Biliary-Pancreatic Sciences* 7 (2000):473-479.
13. Chowdappa R and Challa VR. "Mesopancreas in pancreatic cancer: where do we stand - review of literature". *Indian Journal of Surgical Oncology* 6.1 (2015):69-74.
14. Kayahara M., *et al.* "Lymphatic flow and neural plexus invasion associated with carcinoma of body and tail of the pancreas". *Cancer* 78.12 (1996):2485-2491.
15. Yoshioka H and Wakabayashi T. "Therapeutic neurotomy on head of pancreas for relief of pain due to chronic pancreatitis". *Archives of Surgery* 76 (1958):546-554.
16. Iacobuzio-Donahue CA., *et al.* "The genetic basis of pancreas cancer development and progression: insights from whole-exome and whole-genome sequencing". *Clinical Cancer Research* 18.16 (2012):4257-4265.
17. Longnecker DS., *et al.* "Racial differences in pancreatic cancer: comparison of survival and histologic types of pancreatic carcinoma in Asians, blacks, and whites in the United States". *Pancreas* 21 (2000):338-343.
18. Lowenfels AB., *et al.* "Hereditary Pancreatitis and the Risk of Pancreatic Cancer". *Journal of the National Cancer Institute* 89.6 (1997):442-446.
19. Mori M., *et al.* "A case control study on the risk factors for pancreatic diseases in Kerala, India". *Hepatogastroenterology* 46.25 (1999):25-30.
20. Chari ST., *et al.* "Risk of pancreatic carcinoma in tropical calcifying pancreatitis: an epidemiologic study". *Pancreas* 9.1 (1994):62-66.
21. Howe GR., *et al.* "Cigarette smoking and cancer of the pancreas: Evidence from a population-based case-control study in Toronto, Canada" 47.3 (1991):323-328.

22. Simona Iodice S., *et al.* "Tobacco and the risk of pancreatic cancer: a review and meta-analysis". *Langenbeck's Archives of Surgery* 393 (2008):535-545.

23. NCRP – ncdirindia (2018).

24. Adhoute X., *et al.* "Subsequent resection of locally advanced pancreatic carcinoma after chemoradiotherapy". *Gastroentérologie Clinique et Biologique* 30(2006): 224-230.

25. Yachida S., *et al.* "Distant metastasis occurs late during the genetic evolution of pancreatic cancer". *Nature* 467(2010): 1114-1117.