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

Review Article

Pancreatic Cancer: A Review Of Epidemiology, Pathophysiology, Risk Factor, Clinical Diagnosis And Current Treatment Outcome

R. Mahaprabu*, S. Karpagam Kumara Sundari, K. A. S. Mohammed Shafeeq

Periyar college of pharmaceutical sciences, Trichy.

ARTICLE INFO

Received: 17 July 2024
Accepted: 22 July 2024
Published: 26 July 2024

Keywords:
Pancreatic Cancer, Epidemiology, Risk Factor, Pathophysiology, Clinical Diagnosis and Current Treatment Outcome.

DOI:
10.5281/zenodo.12916538

ABSTRACT

Pancreatic cancer is a highly aggressive malignancy that has poor prognosis, represent one of the most challenging clinical problems in oncology today. This article is a summary of pancreatic cancer epidemiology, risk factors, pathophysiology, diagnosis and therapy. According to epidemiological data, pancreatic cancer is one of the top causes of death from cancer on a worldwide basis and generally presents with an extremely poor five year survival rate largely due to late stage diagnosis. In the development of this condition, risk factors such as genetic susceptibilities of obesity, smoking, chronic pancreatitis further emphasize its complex ethology. Pancreatic adenocarcinoma arises from mutations in several tumor suppressor and oncogene genes, leading to deregulated cellular proliferation and survival. Though, due to advancements in treatment methods such as surgery, chemotherapy and radiation therapy beside targeted therapeutics but still traditional ways for diagnosis laboratory investigations with addition of imaging modalities like Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and endoscopic ultrasonography (EUS) besides evaluation of biomarkers namely CA 19-9 levels. Even the best of them have a very low success rate and therefore there is an urgent need for additional therapeutic options. In this review we discussednovel treatments in immunotherapy and precision medicine which are designed to improve the dismal therapeutic outlook of pancreatic cancer patients with longer survival rates, quality of life and few adverse events.

INTRODUCTION

Pancreatic cancer is one of the leading causes of cancer mortality in developed countries and one of the most lethal malignant neoplasms across the world. Approximately 90% of pancreatic cancers are Pancreatic Ductal Adenocarcinomas (PDAC)

***Corresponding Author:** R. Mahaprabu
Address: *Periyar college of pharmaceutical sciences, Trichy*
Email ✉: mahaprabu1465@gmail.com

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

[1]. This review presents the most upto date knowledge on the incidence, outcomes, risk factors, pathogenesis, diagnostics, and treatments available to Pancreatic Ductal Adenocarcinoma patients (PDAC). Therefore, pancreatic cancer seems to be one of the biggest challenges in tackling the fight against cancer in the 21st century [2]. Despite advancements in biomarker and medical imaging technologies, pancreatic cancer frequently remains undetected until late in the disease's progression, exhibiting vague signs. This includes surgery, chemotherapy, radiation therapy, targeted therapies, and immunotherapy. Minimal disease and surgical resection offer a chance for recovery, however, only a tiny fraction of patients are suitable for surgery with the goal of curing the condition at diagnosis [3]. Chemotherapy protocols like FOLFIRINOX and gemcitabine-based combos have shown efficacy in extending survival, while ongoing research investigates novel therapeutic agents that target particular biochemical pathways and immunological checkpoints to improve outcomes. This review seeks to provide a complete overview of pancreatic cancer and pave the path for improved clinical outcomes and patient treatment in the future by combining existing knowledge and emerging research trends [4]

Epideminology Of Panceratic Cancer

A major worldwide health burden, pancreatic cancer is marked by a difficult prognosis and high death rates. Globally, pancreatic cancer was expected to cause 510,000 new cases and 467,409 deaths in 2022. It is the 12th most common cancer globally. These numbers highlight the seriousness of the illness and how it affects general health.

1. Geographic Distribution and Incidence: The incidence rates of pancreatic cancer vary significantly based on demography and geography. The developed world's greatest incidence rates can surpass 8 cases per 100,000 people annually are found in North America and Europe. In contrast, rates are reported to be lower in parts of Asia and Africa, while some nations are seeing rising trends as their lifestyles become more Westernized [5].

2. Age and Gender Distribution: Most cases of pancreatic cancer occur in older people with those over 60 having the greatest incidence rates. At diagnosis, the median age is approximately 70 years old. Incidence also shows a modest male predominance with men slightly more affected than women [6].

3. Risk Factors: Pancreatic cancer is caused by a number of known risk factors. Tobacco use is the most important modifiable risk factor contributing to 20–25% of cases worldwide. Diabetes mellitus, obesity, chronic pancreatitis, and dietary variables such as a high intake of red meat and processed foods are additional risk factors. A tiny but considerable percentage of cases are caused by inherited genetic disorders, such as abnormalities in genes like Breast Cancer Gene 1 [BRCA1], and Breast Cancer Gene 2 [BRCA2] and familial pancreatic cancer syndrome [7].

4. Molecular Subtypes: Pancreatic cancer comprises multiple molecular subgroups, each with distinct genetic alterations and clinical traits. With almost 85% of cases, Pancreatic Ductal Adenocarcinoma (PDAC) is the most common subtype. The two less common kinds acinar cell carcinomas and Pancreatic Neuroendocrine Tumors (PNETs), differ in their biological characteristics and approaches to treatment [8].

5. Survival Rates: Due to late-stage detection and few effective treatment choices, pancreatic cancer is well-known for having a bad prognosis. It is among the worst cancers globally, with a five-year survival rate of fewer than 10% overall [9]. Depending on the stage at diagnosis, the prognosis differs dramatically localized tumor have a better chance of success than metastatic disease.

Pathophysiology Of Pancreatic Cancer

The multifaceted nature of pancreatic cancer, especially Pancreatic Ductal Adenocarcinoma (PDAC), is attributed to the intricate connections between genetic alterations, tumor microenvironment dynamics, and systemic consequences. It is imperative to comprehend the fundamental pathophysiology in order to progress therapeutic and diagnostic approaches for this difficult cancer [10].

1. Genetic Alterations: A sequence of genetic abnormalities that impair regular cellular function and encourage unchecked growth are the trigger and cause of pancreatic cancer with an activating mutation of the KRAS oncogene found in over 95% of patients, this is the most frequent and early genetic change associated with PDAC. Underlying signalling pathways implicated in cell survival and proliferation are constitutively activated upon KRAS mutation [11].

2. Tumor Suppressor Genes: Tumor suppressor gene inactivation is another important factor in the development of pancreatic cancer, in addition to KRAS. Pancreatic cancer is often associated with TP53, CDKN2A (p16), and SMAD4 mutations or deletions, which can lead to genomic instability, resistance to apoptosis, and metastatic promotion [12]. Tumor growth is aided by the loss of function in these genes, which interferes with DNA repair and cell cycle regulation.

3. Microenvironment and Stromal Interactions: The extracellular matrix proteins, fibroblasts, immune cells, and vasculature that make up the dense desmoplastic stroma of pancreatic tumor are what define them. A barrier that prevents immune cell infiltration and medication administration is formed by the stroma, which also gives the tumor structural support [13]. Immune evasion, tumor development, and invasion are all facilitated by interactions between cancer cells and stromal constituents.

4. Immune Evasion and Tumor Microenvironment: The immunosuppressive microenvironment is produced by pancreatic cancer by a number of methods, such as the production of checkpoint molecules like PD-L1 and the recruitment of regulatory T cells and myeloid-derived suppressor cells. The aggressiveness of the disease is facilitated by these pathways, which also decrease anti-tumor immune responses and encourage immunological evasion [14].

5. Metabolic Reprogramming: To enable their quick development and survival in nutrient- poor environments, pancreatic cancer cells display significant metabolic changes. Pancreatic cancer cells have increased glucose uptake and lactate production even in the presence of oxygen due to improved aerobic glycolysis also known as the Warburg effect. Additional growth advantages for cancer cells come from altered metabolic pathways, such as lipogenesis and glutamine metabolism [15].

6. Systemic Effects and Paraneoplastic Syndromes: Due to the tumor cell's production of hormones, cytokines, and other bioactive chemicals, pancreatic cancer might present with paraneoplastic syndromes and systemic symptoms. Cases in point are venous thromboembolism, cachexia, insulin resistance, and hyperglycaemia brought on by tumor secretion or pancreatic exocrine insufficiency [15].

RISK FACTORS OF PANCREATIC CANCER

A multitude of factors including genetic, environmental, and behavioral can impact the development of pancreatic cancer. Gaining an understanding of these risk factors is essential for early detection, preventative tactics, and enhancing outcomes for high-risk patients [16].

1. Smoking: Approximately 20-25% of pancreatic cancer occurrences worldwide are caused by smoking making it one of the most important modifiable risk factors. There is a dose-

response association between the length and severity of cigarette smoking and the risk of pancreatic cancer, with smokers having a 2-3 times higher risk than non-smokers [17].

2. Obesity and Physical Inactivity: A body mass index (BMI) of 30 kg/m² or more is considered obese and is linked to a higher risk of pancreatic cancer. It has been suggested that insulin resistance and adipose tissue inflammation are the processes that connect obesity to the development of pancreatic cancer. Pancreatic cancer risk is independently influenced by physical inactivity with sedentary behavior being linked to higher incidence rates [18].

3. Chronic Pancreatitis: The chance of developing pancreatic cancer is greatly elevated by chronic pancreatitis, which is defined by ongoing inflammation of the pancreas. The risk is greater in people with familial or chronic pancreatitis, especially in those with mutations in genes such as Serine Protease Inhibitor Kazal Type 1 [SPINK1] and Protease Serine 1 [PRSS1] [19].

4. Diabetes Mellitus: Diabetes mellitus is an early sign of pancreatic cancer as well as a risk factor. Compared to people without diabetes those with diabetes have an adjusted relative risk of roughly 1.5-2.0 times higher for pancreatic cancer if they have had the disease for more than five years [20]. Pancreatic cancer and diabetes may have a reciprocal association, with diabetes linked to pancreatic cancer frequently occurring before the illness is diagnosed.

5. Family History and Genetic Syndromes: Pancreatic cancer raises an individual's risk and may indicate a hereditary susceptibility if there is a family history of the disease. Familial pancreatic cancer syndromes (such as Peutz-Jeghers syndrome) and inherited mutations in genes like BRCA1, BRCA2, and PALB2 are responsible for 5-10% of pancreatic malignancies [21]. Hereditary pancreatitis is another type of inherited genetic syndrome.

6. Dietary Factors: Pancreatic cancer risk is influenced by dietary factors, though precise correlations are less clear than for other malignancies. Increased risk has been associated with poor intake of fruits and vegetables and high consumption of red and processed meats. The impact of dietary fat consumption especially saturated fats remains debatable and needs more research [22].

7. Occupational Exposures: The chance of developing pancreatic cancer may rise if one is exposed to specific occupational carcinogens, such as chemicals used in the metalworking and petroleum refining sectors. Pesticide and herbicide exposure at work has also been linked albeit the data is not as clear-cut.

8. Race and Ethnicity: Incidence and mortality rates of pancreatic cancer differ depending on race and ethnicity in the United States African and American populations had higher rates than Caucasians. Socioeconomic position healthcare access and genetic variables may all have an impact on this difference [23].

Clinical Diagnosis Of Pancreatic Cancer

1. Imaging Modalities

a. Computed Tomography (CT): CT scan is frequently the first imaging modality used to diagnose pancreatic cancer. They include thorough anatomical details regarding the pancreas, it's surrounding structures, and possible metastatic locations. Pancreatic tumors, vascular involvement, and regional lymphadenopathy can all be found with contrast-enhanced CT scans [24].

b. Magnetic Resonance Imaging (MRI): MRI is useful for examining pancreatic cancers, especially when measuring vascular invasion and biliary obstruction. This includes Magnetic Resonance Cholangiopancreatography (MRCP). In those who shouldn't utilize iodinated contrast materials for CT scans, MRI is recommended [25].

c. Endoscopic Ultrasound (EUS): EUS provides a high-resolution image of the pancreas

and surrounding structures by combining endoscopy and high-frequency ultrasound. It makes it possible to biopsy or perform Fine Needle Aspiration (FNA) on worrisome lesions, giving information on both staging and diagnosis [26].

d. Positron Emission Tomography (PET-CT): Radiotracers like fluorodeoxyglucose (FDG) can be used in PET-CT scans to measure the metabolic activity of pancreatic cancers and identify distant metastases. PET-CT is helpful for assessing therapy response and staging pancreatic cancer [27].

2. Biomarkers

a. CA 19-9: The most popular tumor marker for pancreatic cancer is CA 19-9. Increased CA 19-9 levels are linked to more advanced illnesses and can be used to track how well a treatment is working. CA 19-9 can be increased in benign situations and lacks specificity and sensitivity for early-stage illness [28].

b. CEA (Carcinoembryonic Antigen): CEA levels may be elevated in pancreatic cancer, other markers, and imaging modalities for diagnosis and monitoring of pancreatic cancer [29].

c. Liquid Biopsies: Analysis of Circulating Tumor DNA (ctDNA), exosomes, and other biomolecules shed by tumors into blood. High sensitivity and specificity for detecting genetic alterations associated with pancreatic cancer.

3. Tissue Sampling

a. Endoscopic Retrograde Cholangiopancreatography (ERCP): This procedure makes the bile and pancreatic ducts directly visible. It can make tissue samples for the histological identification of pancreatic lesions using brush cytology or FNA easier [30].

b. Biopsy by Fine-Needle Aspiration (FNA): FNA biopsy enables the extraction of tissue samples from worrisome lesions or pancreatic masses under the supervision of EUS or CT scan. Tumor grade and subtype can be ascertained and a conclusive diagnosis can be made using histopathological analysis of FNA specimens [31].

4. Emerging Technologies

a. Liquid Biopsy: This technique examines blood or other bodily fluids for the presence of biomarkers such as Cell-Free DNA (cfDNA), Circulating Tumor Cells (CTCs), and other substances. In pancreatic cancer, liquid biopsy shows promise for minimal residual disease identification, treatment response monitoring, and early detection [32].

b. Artificial Intelligence (AI) and Machine Learning: To increase the precision and effectiveness of pancreatic cancer diagnosis, AI-based algorithms are being used to imaging and biomarker data. These technologies could help with patient risk assessment and early diagnosis [33].

Current Treatment Of Pancreatic Cancer

Treatment options for pancreatic cancer are limited and the disease is frequently identified at an advanced stage, making it a tough condition to treat. Surgery, chemotherapy, radiation therapy, targeted treatments, immunotherapy, and supportive care are all part of the multimodal approach used in current pancreatic cancer treatment protocols. Novel therapy options targeted at improving patient outcomes have been developed as a result of advances in understanding the genetics and molecular mechanisms of pancreatic cancer.

1. Surgical Treatment

a. Pancreaticoduodenectomy (Whipple Procedure): The main surgical method for treating tumors in the pancreatic head is the Whipple surgery. The pancreatic head, duodenum, gallbladder, part of the bile duct, and occasionally the stomach are all removed during the procedure. In cases of pancreatic cancer, surgery is the only treatment option available, but only those with a confined disease and good performance status are eligible [34].

b. Distal Pancreatectomy: Distal pancreatectomy may be used to treat cancers that are in the body or in the pancreatic tail. During this operation, the pancreatic head and duodenum are left intact, but the organ's body and tail are removed. Adjuvant or neoadjuvant therapy may be used in conjunction with surgery to enhance results [35].

2. Chemotherapy

a. First-Line Chemotherapy: A common first-line chemotherapy treatment for advanced pancreatic cancer in the past has been gemcitabine. Folinic acid, Fluorouracil, Irinotecan, and Oxaliplatin [FOLFIRINOX] has been demonstrated in recent studies to produce better results in certain locally advanced disease cases as well as in patients with good performance status [36].

b. Second-Line Chemotherapy: The options for patients who do not respond to first-line therapy include gemcitabine combined with nab-paclitaxel or Nanoliposomal Irinotecan (nal-IRI) combined with fluorouracil and leucovorin. In the second-line situation, these regimens have demonstrated efficacy in improving survival outcomes [37].

3. Radiation Therapy

a. External Beam Radiation Therapy (EBRT): The locally advanced pancreatic cancer, EBRT may be used in conjunction with chemotherapy (chemo-radiation) or as an adjuvant therapy following surgery to lower the chance of local recurrence. Radiation therapy techniques like stereotactic body radiation therapy (SBRT) spare surrounding healthy tissues while administering high doses of radiation to the tumor [38].

b. Stereotactic Body Radiation Therapy (SBRT): Stereotactic Body Radiation Therapy (SBRT) is emerging as an effective treatment for pancreatic cancer, offering an advantage in both survival and quality of life. SBRT delivers high doses of radiation in a few sessions, precisely targeting the tumor while sparing surrounding tissue. This method is particularly beneficial for patients with locally advanced or borderline respectable pancreatic cancer, providing better local control and shorter treatment duration compared to conventional radiotherapy [39].

4. Targeted Therapies

a. Epidermal Growth Factor Receptor (EGFR) Inhibitors: The advanced pancreatic cancer, EGFR inhibitors like erlotinib have been investigated in combination with chemotherapy. However, patient selection based on biomarkers is critical, and their clinical impact is minimal [40].

b. Poly (ADP-ribose) Polymerase (PARP) Inhibitors: Patients with germline BRCA mutations have demonstrated the effectiveness of PARP inhibitors, such as olaparib [41]. These drugs have shown therapeutic effects in a subset of pancreatic cancer patients by taking advantage of flaws in DNA repair pathways.

5. Immunotherapy

a. Checkpoint Inhibitors: As a monotherapy, immune checkpoint inhibitors that target the PD-1/PD-L1 and CTLA-4 pathways have demonstrated a limited degree of efficacy in pancreatic cancer. To improve anticancer immune responses, combination approaches with chemotherapy or other immunomodulatory are the subject of ongoing study [42].

b. Adoptive cell treatments and cancer vaccines: The ability of adoptive cell therapies, such as chimeric antigen receptor (CAR) T-cell therapy, and cancer vaccines, like GVAX, to elicit particular antitumor immune responses in pancreatic cancer are available [43].

6. Supportive Care

a. Pain Management: One of the main signs of pancreatic cancer is pain. In order to enhance the quality of life, management consists of supportive care techniques in addition to pharmacological interventions such as opioids and nerve blocks [44].

b. Nutritional Support: Because of pancreatic exocrine insufficiency and cancer cachexia, pancreatic cancer can result in malnutrition. Maintaining nutritional status requires nutritional care, which includes dietary advice and enzyme replacement treatment [44].

Future Research Recommendation:

1. Early Detection and Screening: Improving methods for early detection of pancreatic cancer when it is more treatable. This includes the development of biomarkers and imaging techniques that can detect the disease at earlier stages, potentially leading to better outcomes [45].

2. Targeted Therapies: Explore targeted therapies based on genetic profiling and molecular characteristics to improve treatment efficacy and reduce side effects.

3. Prevention Strategies: Further understand the role of lifestyle factors (smoking cessation, diet modification) and screening programs in reducing the incidence and improving outcomes.

4. Personalized Medicine: Develop personalized treatment approaches based on the unique genetic and molecular profiles of individual tumors to optimize treatment outcomes.

5. Patient Care and Support: Enhance supportive care strategies to manage symptoms, improve quality of life, and provide psychosocial support for patients and their families throughout the treatment journey.

6. Immunotherapy: Advancements in immunotherapy aim to harness the body's immune system to target and destroy pancreatic cancer cells more effectively. This includes checkpoint inhibitors, CAR-T cell therapy, and therapeutic vaccines designed to enhance the immune response against tumors [46].

7. Precision Medicine: Tailoring treatment based on the specific genetic mutations and molecular characteristics of individual tumors. This approach involves identifying biomarkers that predict response to targeted therapies and developing personalized treatment plans accordingly.

8. Targeted Therapies: Continued research into targeted therapies that inhibit specific pathways involved in pancreatic cancer growth and progression. Examples include drugs targeting the KRAS mutation, which is prevalent in pancreatic cancer, as well as inhibitors of other key signaling pathways [47].

9. Combination Therapies: Exploring the synergistic effects of combining different treatment modalities such as chemotherapy, radiation therapy, targeted therapies, and immunotherapy. Combination approaches aim to maximize treatment efficacy while minimizing side effects [48].

10. Liquid Biopsies and Monitoring: Utilizing liquid biopsies (circulating tumor DNA and other biomarkers in blood) for non-invasive monitoring of treatment response and disease progression. This approach may enable more frequent monitoring and early detection of treatment resistance.

11. Supportive Care and Quality of Life: Enhancing supportive care strategies to manage symptoms and improve the quality of life for pancreatic cancer patients undergoing treatment. This includes palliative care and supportive therapies that address pain, nutrition, and psychosocial aspects of care [49].

12. Clinical Trials and Collaborative Research: Increasing participation in clinical trials to test new therapies and combinations. Collaborative research efforts across institutions and international collaborations are crucial for advancing understanding and treatment options for pancreatic cancer [50].

Summary Of Pancreatic Cancer

The prognosis for pancreatic cancer is quite dismal, making it a dreadful illness. Its aggressiveness and late-stage detection make it one of the deadliest tumors. Pancreatic ductal

adenocarcinoma (PDAC) is the most common form. The frequency of pancreatic cancer varies worldwide, with wealthier nations having higher rates of the disease. Among the risk factors are specific genetic mutations, diabetes, obesity, smoking, and chronic pancreatitis. Most of the patients receive an advanced diagnosis [15]. Imaging methods such as CT, MRI, and endoscopic ultrasonography (EUS) are used in diagnosis, and EUS-guided fine-needle aspiration (FNA) is used in biopsy confirmation [21]. The diagnosis, biomarkers such as CA 19-9 are not conclusive. Palliative care, chemotherapy, radiation therapy, and surgical excision are all part of the treatment [25]. While it is achievable in a small percentage of cases, surgery, such the Whipple technique, offers a potential solution. Standard treatment options include gemcitabine-based medicines or chemotherapy regimens like FOLFIRINOX, while immunotherapy and targeted therapies are gaining popularity. Improved knowledge of the tumor microenvironment and molecular biology is essential for creating more effective therapies [32]. Better diagnostic and treatment approaches are desperately needed for pancreatic cancer, which continues to be a significant clinical issue [30]. Additional retrospective research identifying people who have had this treatment and the results related to it will contribute to the body of evidence and assist in developing guidelines for the future.

Outcome

Pancreatic cancer patients have a 5-year survival rate of about 6% globally, however, published literature reports a range of 2% to 9%. A few of the factors that affect survival are age, sex, co-morbidities, quality of healthcare provided, and lifestyle choices; these factors also contribute to the variation in survival rates within nations [2]. At the moment of diagnosis, the tumor stage is the primary determinant influencing the course of the disease Five-year survival rates are reported to be 27% for patients who are able to undergo effective surgical resection; in contrast, the median survival rates for patients with locally progressed or metastatic illness are two and six months, respectively. Although there has been some progress in the surgical and medicinal management of pancreatic cancer, the 5-year survival rates have not increased significantly. The need to find ways to screen high-risk patients, create early detection techniques, and enhance the surgical and medical care of these patients is underscored by the increasing prevalence and persistently low survival rates [4].

CONCLUSION

Pancreatic cancer is characterized by its rapid progression, delayed discovery, and limited therapy choices, making it one of the most challenging diseases to treat. Despite advancements in our understanding of its molecular causes and therapeutic methods, pancreatic cancer still has a dismal overall prognosis, with a five-year survival rate of roughly 10%. A primary factor that negatively impacts pancreatic cancer prognosis is delayed diagnosis. This emphasizes the urgent need for improved early detection techniques, like the development of biomarkers and state of the art imaging methods that can detect pancreatic cancer at earlier, potentially curable stages. Standard treatment methods include surgery, chemotherapy, radiation therapy, and immunotherapy. Recent advances in genomic profiling have led to the discovery of important genetic anomalies that contribute to the development of pancreatic cancer. The tumor microenvironment's immunosuppressive properties have rendered immunotherapy a challenging treatment option for pancreatic cancer. It has shown to be a viable new treatment option for cancer. Collaborative review initiatives including innovative therapy modalities and clinical trials evaluating novel drug combinations will be essential in the future to advance pancreatic

cancer treatment. Continued support for studies enhancing outcomes and ultimately extending the survival time of pancreatic cancer patients requires interdisciplinary teamwork and patient-centred care.

REFERENCE

1. Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic adenocarcinoma, version 2.2021, NCCN Clinical Practice Guidelines in Oncology. 2021; 19(4):439-457.
2. Neoptolemos JP, Kleeff J, Michl P, et al., Therapeutic developments in pancreatic cancer: current and future perspectives. 2018; 15(6): 333-348.
3. Rawla P, Sunkara T, Gaduputi V. Epidemiology of pancreatic cancer: global trends, etiology and risk factors. 2019; 10(1): 10-27.
4. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. 2014; 74(11):2913-2921.
5. Bray F, Ferlay J, Soerjomataram I, et.al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. 2021; 71(3): 209-249.
6. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020; 70(1):7-30.
7. Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. 2015; 44(1):186-198.
8. Duel EJ, Lucenteforte E, Olson SH, et al., Pancreatitis and pancreatic cancer risk: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium. 2012; 23(11):2964-2970.
9. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. 2014; 371(11):1039-1049.
10. Biankin AV, Waddell N, Kassahn KS, et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. Nature. 2012; 491(7424):399-405.
11. Waddell N, Pajic M, Patch AM, et al., Whole genomes redefine the mutational landscape of pancreatic cancer. 2015; 518(7540):495-501.
12. Neesse A, Algül H, Tuveson DA, et al., Stromal biology and therapy in pancreatic cancer: a changing paradigm. 2015; 64(9):1476-1484.
13. Beatty GL, Winograd R, Evans RA, et al. Exclusion of T cells from pancreatic carcinomas in mice is regulated of extratumoral macrophages. 2015; 149(1):201-210.
14. Ying H, Kimmelman AC, Lyssiotis CA, et al., Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. 2012; 149(3): 656-670.
15. Gukovskaya AS, Pandol SJ. Cell death pathways in pancreatitis and pancreatic cancer. 2004; 4(6):567-586.
16. Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. Int J Epidemiol. 2015; 44(1):186-198.
17. Bosetti C, Lucenteforte E, Silverman DT, et al., Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium. 2012; 23(7):1880-1888.
18. Patel AV, Rodriguez C, Bernstein L, et al., Obesity, recreational physical activity, and risk of pancreatic cancer in a large U.S. cohort. 2005; 14(2): 459-466.
19. Kirkegard J, Mortensen FV, Cronin-Fenton D. Chronic pancreatitis and pancreatic cancer risk: a systematic review and meta-analysis. 2017; 112(9):1366-1372.

20. Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. 1995; 273(20): 1605-1609.
21. Aune D, Greenwood DC, Chan DS, et al., Body mass index, abdominal fatness, and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. 2012; 23(4): 843-852.
22. Schenk M, Schwartz AG, O'Neal E, et al. Familial risk of pancreatic cancer. J Natl Cancer Inst. 2001; 93(8): 640-644.
23. Al-Hawary MM, Francis IR, Chari ST, et al., Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. 2014; 270(1): 248-260.
24. Tamm EP, Balachandran A, Bhosale PR, et al., Imaging of pancreatic adenocarcinoma: update on staging/ resectability. 2012; 50(3): 407-428.
25. Dumonceau JM, Polkowski M, et al., Indications, results and clinical impact of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline 2011; 43(10): 897-912.
26. Heinrich S, Goerres GW, Schäfer M, et al., Positron emission tomography/computed tomography influences on the management of resectable pancreatic cancer and its cost-effectiveness. Ann Surg. 2005; 242(2): 235-243.
27. Ballehaninna UK, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis, and management of pancreatic adenocarcinoma: an evidence-based appraisal. J Gastrointest Oncol. 2012; 3(2): 105-119.
28. Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. 2006; 24(33): 5313-5327.
29. Baron TH, DiMaio CJ, Wang AY, et al., American Gastroenterological Association Clinical Practice Update: management of pancreatic necrosis. 2020; 158(1): 67-75.
30. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011; 364(19):1817-1825.
31. Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic adenocarcinoma, version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021; 19(4):439-457.
32. Cameron JL, He J. Two thousand consecutive pancreaticoduodenectomies. J Am Coll Surg. 2015; 220(4):530-536.
33. Hebert-Magee S, Bae S, Varadarajulu S, et al. The presence of a cytopathologist increases the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration cytology for pancreatic adenocarcinoma: a meta-analysis. 2013; 24(3):159-171.
34. Huguet F, Goodman KA, Azria D, et al. Radiotherapy technical considerations in the management of locally advanced pancreatic cancer: American-French consensus recommendations. Int J Radiat Oncol Biol Phys. 2012;83(5):1355-1364.
35. Cohen JD, Javed AA, Thoburn C, et al., Combined circulating tumor DNA and protein biomarker-based liquid biopsy for the earlier detection of pancreatic cancers. 2017; 114(38): 10202-10207.
36. Wang X, Li F, Zhou X, et al., Application of artificial intelligence in the diagnosis of pancreatic cancer. 2020; 471: 17-23.
37. Ferrone CR, Marchegiani G, Hong TS, et al., Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX

38. for locally advanced and borderline resectable pancreatic cancer. 2015; 261(1): 12-17.
39. Conroy T, Hammel P, Hebbar M, et al., FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. 2018; 379(25): 2395-2406.
40. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017; 357(6349):409-413.
41. Von Hoff DD, Ervin T, Arena FP, et al., Increased survival in pancreatic cancer with nab- paclitaxel plus gemcitabine. 2013; 369(18): 1691-1703.
42. Reilly EM, Lee JW, Lowery MA, et al., Phase 1 trial evaluating cisplatin, gemcitabine, and veliparib in 2 patient cohorts: germline BRCA mutation carriers and wild-type BRCA pancreatic ductal adenocarcinoma. 2018; 124(7): 1374-1382.
43. Moningi S, Dholakia AS, Raman SP, et al., The role of stereotactic body radiation therapy for pancreatic cancer: a single-institution experience. 2015; 22(7): 2352-2358.Ghaly, M.; Gogineni, E.; Saif M.W. The Evolving Field of Stereotactic Body Radiation Therapy in Pancreatic Cancer. 2019, 3, 9-14.
44. Golan T, Hammel P, Reni M, et al., Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. 2019; 381(4):317-327.
45. Le DT, Durham JN, Smith KN, et al., Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. 2017; 357(6349): 409-413.
46. Collisson EA, Bailey P, Chang DK, et al., Molecular subtypes of pancreatic cancer. Nat Rev Gastroenterol Hepatol. 2019; 16(4): 207-220.
47. Ryan DP, Hong TS, Bardsey N. Pancreatic adenocarcinoma. N Engl J Med. 2014; 371(11): 1039-1049.
48. Kaur S, Baine MJ, Jain M, Sasson AR, Batra SK. Early diagnosis of pancreatic cancer: challenges and new developments. Biomarkers Med. 2012; 6(5): 597-612.
49. Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic adenocarcinoma, version 2.2021, NCCN clinical practice guidelines in oncology. 2021; 19(4): 439-457.
50. Waddell N, Pajic M, Patch AM, et al., Whole genomes redefine the mutational landscape of pancreatic cancer. 2015; 518(7540): 495-501.

HOW TO CITE: R. Mahaprabu*, S. Karpagam Kumara Sundari, K.A.S. Mohammed Shafeeq, Pancreatic Cancer: A Review Of Epidemiology, Pathophysiology, Risk Factor, Clinical Diagnosis And Current Treatment Outcome, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 7, 1896-1906. https://doi.org/10.5281/zenodo.12916538