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A Study on Pancreatic Ductal Adenocarcinoma

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Abstract. Pancreatic cancer, particularly pancreatic ductal adenocarcinoma (PDAC), remains one of the deadliest cancers despite decades of development, with extremely low 5-year survival rates. Its lethality is driven by late diagnosis, aggressive tumor biology, and limited therapeutic options during metastatic settings. Although this cancer can be easily cured if detected early, it rarely produces symptoms at early stages, preventing the victim from seeking help in the first place. Risk indicators for this cancer include high age, increased usage of unhealthy substances such as drugs, alcohol, and cigarettes, and the inheritance of mutations associated with PDAC. In this paper, the symptoms, prognosis, past and future treatments, diagnostic modalities, and epidemiological insights are discussed. Particularly, since pancreatic cancer's treatment revolves so much around earlier diagnoses, evolving methods of imaging and scanning pancreatic ductal adenocarcinoma will also be revealed. Additionally, this paper details the future prognosis of this disease's cure, including implementation of AI, endoscopic ultrasound, and next-generation biomarkers compared to the current standards such as chemotherapy, targeted therapy, and immunotherapy. By integrating historical context with cutting-edge developments, this paper underscores the need for earlier detection, more effective interventions, and smarter diagnostic tools to improve patient outcomes in this formidable disease.

Keywords: Pancreatic Ductal Adenocarcinoma (PDAC), risk, metastasis, diagnosis

1. Introduction

Pancreatic cancer ranks among the most lethal cancers worldwide, mainly because of late diagnoses leading to high rates of metastasis. Incidence and mortality are closely matched, owing to dismal survival—often quoted at under 10% at five years [1]. In Western countries, it is projected to become a leading cause of cancer-related death within the next decade. The predominant type of pancreatic cancer, PDAC, often presents late with non-specific symptoms like weight loss, jaundice, loss of appetite and weight, light colored stools, dark urine, and changes in bowel habits. Over half of known PDAC cases show metastasis at diagnosis, causing symptoms including swelling, weakness, unexplained weight loss, ascites, nausea, very severe belly pain, and extreme fatigue [1].

Risk factors include smoking, obesity, diabetes, chronic pancreatitis, and hereditary syndromes such as BRCA1/2 mutations or Lynch syndrome [1]. Early detection occurs rarely due to the cancer being asymptomatic in early stages and the absence of effective, efficient, and lowcost population-wide screening methods [2].

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This paper begins by tracing the evolution of diagnostic modalities and treatments, then delves into current standard therapies. It examines the intricacies of pancreatic cancer biology, discusses the emerging role of artificial intelligence (AI) in diagnostics, and concludes with future expectations, including biomarker-driven precision care and technological innovation.

The significance of this review lies in presenting the current challenges and information on pancreatic cancer. With many risk factors increasing the rate of pancreatic cancer, being aware is extremely important. Also, the newer treatments presented in this review will potentially be able to cure this cancer, so being aware of them is also important.

2. Tumor biology and risk context

PDAC is driven by chromosomal alterations, genetic mutations (e.g., KRAS, TP53), desmoplastic stroma, and unusual miRNA regulation [3]. Additional dietary factors can increase one's chances of contracting PDAC, such as diets high in red/processed meats, sugars, and saturated fats increase risk, whereas Mediterranean or plant-based diets, tea and coffee consumption, and certain micronutrients (vitamins, minerals) are generally associated with lower risk.

Once started, pancreatic cancer almost always begins within the ductal cells of the pancreas, causing an overgrowth of cancer cells in that one spot. Because this growing tumor is located deep within the pancreas, its formation is not obvious initially. From there, it travels along the membrane of ductal cells until it's overtaken almost the entirety of the inside of the pancreas [1]. After that, it moves on to metastasis, where it utilizes tubes such as the superior mesenteric artery, portal vein, bile ducts, and the duodenum to move to other parts of the body, wreaking havoc and causing the body to lose function [3]. Once metastasis begins, survival rates drop drastically.

3. Evolution of diagnosis and treatment

Historically, surgical resection via the Whipple procedure (pancreaticoduodenectomy) has been the only potential treatment for pancreatic ductal adenocarcinoma (PDAC)that could cure this cancer, but fewer than 20% of PDAC patients are eligible at diagnosis, and even among for those who undergoing this surgery, five-year survival hovers around 21% anyways, rendering this treatment impractical and ultimately ineffective [4-6]. Adjuvant chemotherapy with fluorouracil initially became a standard following surgery, later supplemented or replaced by gemcitabine for unresectable disease, which modestly improved survival. However, both treatments were costly despite their ineffectiveness. The average Whipple procedure ranges from 50,000 USD to 100,000 USD, and chemotherapy costs from 7,000 USD to 10,000 USD for each session [7]. Combined modality approaches, such as chemoradiation in locally advanced diseases, offered incremental benefits. Over time, systemic chemotherapy regimens evolved; newer combinations such as FOLFIRINOX and gemcitabine–nabpaclitaxel have shown better efficacy, though they remain palliative in most advanced cases [8]. More recently, immunotherapies and targeted therapies, including experimental chimeric antigen receptor macrophages targeting cMET, are being explored preclinically [5]. While targeted and immunotherapies have been utilized in the past, they were also not practical treatments given their either low success rate or low applicability rates combined with low population. Furthermore, the standard chemotherapy treatments are extremely impractical for the treatment of pancreatic cancer given the extremely severe side effects that cannot be handled by the elderly, which is the cancer's main target.

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4. Current standards of care

There are a variety of current modalities and challenges with the current diagnoses of PDAC. Multi-director CT using MRI has been frequently employed to initially detect and diagnose cancer, and it is the longest standing method of detection. Unfortunately, this method still lacks a sufficiently high success rate However, two new methods of discovering PDAC are Endoscopic Ultrasound and Biomarkers [9]. Endoscopic Ultrasound, or EUS, combines endoscopy with ultrasound technology to create detailed images of the digestive tract and surrounding organs that could potentially reveal any PDAC tumors. On the other hand, biomarkers are currently being tested for use. Biomarkers is the use of a molecule to see the minimum concentration needed for visible inhibition, which can be used through the detection of changes in these biomarkers [10].

5. New experimental treatments

One emerging treatment for pancreatic ductal adenocarcinoma is Claudin 18.2 Targeted Therapy [11]. Claudin 18.2 is a junction protein that is usually only found in gastric mucosa. However, in PDAC tumors, it is present in every single cell. Due to its scarcity within healthy cells and high frequency within cancer cells, it is a prime target for targeted therapy. The creation of antibodies that target the Claudin 18.2 protein will be able to destroy the cancer with great effectiveness without causing significant side effects. This alleviates one of the practical issues revolving around cancer treatments for PDAC, which is that the side effects of treatments may be too severe for the age group that the cancer targets (people 60+) [11]. When an antibody targeting Claudin 18.2 is attached to a tumor cell, it can have two effects, both of which are positive. First, it can signal the immune cells, such as B cells and cytotoxic T cells, which formerly may have been blind to these tumor cells, to attack them and kill them. Alternatively, the antibody can kill the tumor cell itself by promoting cell lysis through the activation of the membrane attack complex. Another benefit to utilizing Claudin 18.2 as a target for treatment is that it can also aid in the diagnosis, since any PDAC tumor, no matter how small, will have significantly higher levels of Claudin 18.2 than any other health tissue, allowing for feasible detection [11]. However, this treatment still has some setbacks. Treatments targeting Claudin cannot penetrate dense stroma, which could significantly inhibit its effectiveness [12]. Also, the gastric mucosa may also unintentionally be targeted, making this treatment still cause side effects, albeit at a much lower degree to treatments like chemotherapy. Finally, if the treatment isn't done right, the immune system could potentially be overactivated, leading to significant harm to the body.

Another new treatment for PDAC is the employment of CAR macrophages to pierce dense tumors and kill the cancer cells. Through significant testing, CAR macrophages have been found to be significantly more effective at infiltrating solid and thick tumors, which is usually the case for those who have experienced metastasis [12]. Therefore, this novel treatment presents a way for even those with extremely large tumors to survive. CAR-M (CAR macrophage) therapy mainly surrounds engineering a patient's existent macrophages to recognize a specific antigen on PDAC [13]. Once successfully engineered, the macrophages will become activated once they meet the cancer cell, allowing them to swallow the cancer cells and digest them through phagocytosis. Furthermore, the genetically engineered macrophages are immune to being modified by PDAC tumors. Normally, to avoid being attacked by macrophages, tumors reprogram these immune cells to be unable to detect them. However, the modifications made to CAR-M protect them from being reprogrammed, allowing them to continually be effective. Not only that, but the modified macrophages also release a chemical that reprograms the other macrophages that were deactivated by the tumor and re-

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activates them, allowing for an even more effective immune response against PDAC. Unfortunately, this treatment still has drawbacks. Firstly, because macrophages have limited reproductive capability, the treatment will take more time than other treatments. Secondly, the chemicals that reactivate macrophages can also activate unneeded immune responses, causing inflammation and immune system overreactions, leading to other complications. In addition, its long-term safety is very unclear, given the novelty of this treatment.

6. Emerging technologies and future directions

One new, rapidly evolving cancer detection technique with extremely high potential is artificial intelligence. Because early diagnosis is so critical for pancreatic cancer, the development of this tool could save thousands of lives [14]. AI effectively utilizes existing tools of diagnosis, except without human error or the need for training. There are two contexts in which artificial intelligence can be used: analyzing existent MRI/CT scans and integrating with blood-based biomarkers. MRI and CT scans, which can be used to detect cancer tumors, are often wasted due to humans not being able to detect miniscule changes. AI algorithms can distinguish lesions and tumors with startling accuracy, allowing for earlier diagnosis, which drastically increases five-year survival rate [15]. On the other hand, AI can also be integrated into blood-based biomarkers. In this context, artificial intelligence has been trained to detect patterns in metabolism, protein levels, and genetic mutations. Combined with data from past patients, the AI can successfully determine if the patient has biomarkers correlated with high cancer risk. As a result, it can solve one of the issues that cause late diagnosis of pancreatic cancer, which is that early-stage pancreatic cancer isn't as externally visible. Utilizing training data from thousands of past diagnoses, artificial intelligence, in the operation of medical equipment, can be much more efficient and cost-effective than actual doctors. Furthermore, artificial intelligence can be employed at any time. For example, AI-assisted robotic surgeries for pancreatic cancer showed a 25% reduction in operative time and a 30% reduction in complications during surgeries [16].

Pancreatic cancer remains a formidable challenge, since its biology is aggressive, detection is usually late and well into metastasis, and curative treatment is only applicable to a minority of people. Progress in systemic therapies has been extremely minor, with medical red tape forcing novel immunotherapies and cellular approaches like CARM targeting cMET to be under investigation. Similarly, molecular profiling, miRNAs, and other biomarkers may pave the way for personalized medicine but are still delayed due to lack of funding and red tape. Hopefully, new medical advancements will allow for a cure to this cancer.

7. Conclusion

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest malignant diseases worldwide. The reasons for this are the absence of specific symptoms in the early stage, delayed diagnosis, and high metastasis rates. Current treatment is limited and there are both economic and physiological burden, especially for elderly patients. Despite the advancement in imaging technology and early detection of biomarkers, the overall detection rate is still unsatisfactory. New targeted therapies (such as Claudin 18.2 antibody) and cellular immune strategies (such as CAR-M therapy) have shown potential to improve treatment specificity, reduce side effects, and overcome tumor barriers. However, these methods are still in the research stage and face technical bottlenecks as well as uncertainty about safety. In the future, it is urgent to combine both prevention and treatment of PDAC from multiple aspects: improve the screening of high-risk groups and the accuracy of early

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diagnosis methods; second, promote the clinical practice of targeted and immunotherapy and optimize drug delivery strategies; in addition, integrate interdisciplinary efforts such as molecular biology and AI to achieve personalized and precise medicine. Only in this way can major breakthroughs be achieved, prolonging patient survival and improving patients' quality of life.

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