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The Role of Liquid Biopsy in Early Detection and Management of Pancreatic Cancer

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ABSTRACT: Pancreatic cancer (PC) has a poor prognosis largely due to detection at a late stage, which limits effective treatment options. This secondary analysis reviews liquid biopsy in the early detection and management of PC, since improving survival outcomes requires earlier detection. Liquid biopsy may identify small tumors early and enable analysis of circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and other biomarkers. The noninvasive nature allows repeated sampling and continuous surveillance. A thorough review of research articles and clinical studies reveals that liquid biopsy may help determine treatment options, recurrence rates, survival outcomes, tumor monitoring, and early detection. Levels of ctDNA, KRAS, PLF, and CTC-AXL and their presence (+/–) indicate prognosis and survival outcome, with positive levels showing poor prognosis. Its noninvasive nature also guides treatment strategies, and ctDNA may determine recurrence pre- or post-surgery. Although studies are still being conducted, liquid biopsy shows promise as a supplementary tool for early detection and tumor monitoring and could be combined with AI or imaging to improve detection rates and patient outcomes.

KEYWORDS: Biomedical and Health Sciences, Immunology, Pancreatic Cancer, Early Detection, Liquid Biopsy.

Introduction

Pancreatic cancer occurs in the pancreas, a gland approximately 6 inches in length, between the stomach and spine, which regulates digestion through the secretion of enzymes and regulates blood glucose via insulin and glucagon production. Pancreatic Ductal Adenocarcinoma (PDAC) is the most common PC, with over 90% of patients showing a mutation in the KRAS oncogene. PDAC is one of the deadliest cancers and is estimated to become the second-leading cause of cancer-related death by 2030.[1] Due to an atypical early stage, PDAC is often detected very late, when limited treatment options lead to a 5-year survival rate of 13%.[2]

Effective treatment options and early detection methods are essential for improving PC prognosis and survival rates. Early symptoms like fatigue and weight loss are often ignored.[3] If the tumor is limited to the pancreatic ducts and is around Stage I, 5-year survival rates may reach up to 80.4%, in some cases.[4] Despite advances in detection and treatment methods, 10% - 20% of patients are diagnosed in the metastatic stage when the cancer has spread throughout organs and vasculature, leading to poor survival outcomes.[3] Thus, an improvement in early detection may lead to better survival rates since more treatment options could be available.

Liquid biopsy is a noninvasive test that analyzes circulating tumor cells (CTCs) and tumor-derived material, such as circulating tumor DNA (ctDNA) in body fluids like blood, stool, saliva, and urine. It provides a convenient and repeatable means for continuous monitoring. It could be applied in early diagnosis and management of PC, including personalizing treatment, monitoring tumor growth and recurrence, and estimating survival rates.[5] Liquid biopsy may detect tumor-derived biomarkers that could indicate early disease, even when tumors are not yet visible on imaging.[4]

This review highlights liquid biopsy as an emerging tool for early detection and management of PC. It focuses on how liquid biopsies may ameliorate early detection and treatment methods and explores the benefits and challenges of liquid biopsies. PC is one of the deadliest cancers, not solely due to the lack of treatment methods, but largely due to late detection associated with its asymptomatic early stage. Standard imaging techniques have trouble detecting PC during its early stage, which leads to limited treatment options in the future when it is too late. Liquid biopsy may offer a promising approach for improving early detection and opening up more treatment options.

Methods

The purpose of this review is to examine how liquid biopsy may improve early detection, tumor monitoring, treatment modalities, and survival outcomes for PC patients. This review article is a qualitative secondary analysis of published data and completed or ongoing trials, consisting of 36 sources total. Journal articles were systematically searched using PubMed, Google Scholar, and Litmaps, while clinical studies were identified using ClinicalTrials.gov. Ethnic and demographic data were obtained using the NIH website. Studies from 2020 to 2025 were included to ensure the inclusion of recent research. The following keywords were used to locate relevant articles: Pancreatic Cancer, Liquid Biopsy, ctDNA, CTC cells, Early Detection, Immunology, Biomedical and Health Sciences, and Pancreatic Cancer Treatment. Inclusion criteria consisted of studies related to PC that involved liquid biopsy for early detection, monitoring, or treatment applications. Only studies published in English were included. Exclusion criteria consisted of studies without the specified keywords, non-peer-reviewed sources such as blogs and opinion pieces, and studies related

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to cancers other than PC. This review focuses on the scope of liquid biopsy rather than providing a detailed discussion of standard treatment strategies. Instead, it shows the potential of liquid biopsies in the early detection and management of pancreatic cancer. As this review focused on the advancement and scope of liquid biopsy in clinical application, there may be potential bias toward highlighting the positives of liquid biopsy over its limitations. Because this study is a literature review and did not involve human subjects, formal ethical approval was not required. Flowcharts, diagrams, or illustrations were created using BioRender.

PC Types, Causes (genetic association), Current Treatment Strategies, and Clinical Outcome:

Types of PC:

The two types of PC are endocrine tumors (also known as neuroendocrine tumors) and exocrine tumors. These types are formed based on the tumor origin. Endocrine tumors begin in the endocrine cells located in the pancreas. On the other hand, exocrine tumors arise from the ducts and glands of the pancreas. Pancreatic Ductal Adenocarcinoma (PDAC) is an exocrine tumor and one of the most common PCs.6 90% of patients express the KRAS oncogene mutation (Figure 1).[1]

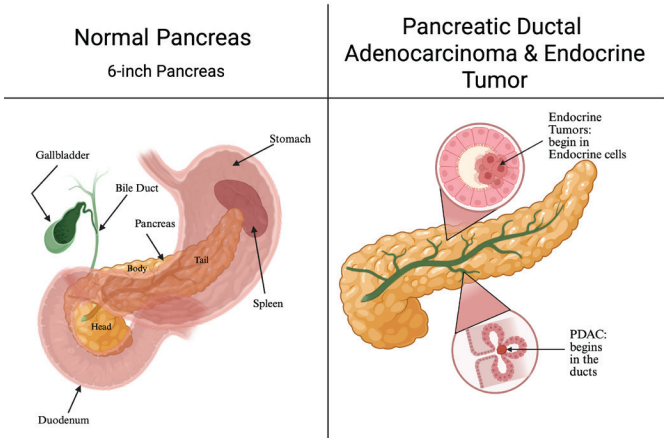

Figure 1: Normal versus cancerous pancreas. This illustration compares a healthy pancreas with one affected by PDAC and endocrine tumors, showing tumor growth, tumor location, and duct obstruction (Created using BioRender).

PDAC is the most aggressive and fatal PC due to its asymptomatic early stage, late detection, thick stroma, and the utilization of autophagy. Detection in the metastatic stage limits treatment options. The thick stroma surrounding the tumor acts as a shield and prevents any drug or medication from entering the tumor microenvironment (TME). Activating mutations in KRAS, along with alterations in TP53, SMAD4, and CDKN2A, allow the tumor to grow rapidly without control. With the help of autophagy, cancer cells have a self-repair and recycling system that allows them to survive with low nutrients and oxygen.[7]

Epidemiology and Risk Factors:

The average diagnosis age for PC is 65 years in the United States, but cases are rising in young women. PC is mainly diagnosed in African American individuals (15.9%), followed by White (13.4%), Hispanic (12.2%), and Asian individuals (10.3%).[8]

In most cases, the cancer occurs at the head of the pancreas rather than the body or tail. The most common symptoms include decreased appetite, indigestion, pale stool, dark urine, jaundice, fatigue, back pain, and abdominal pain. However, these are general symptoms that are often taken for granted, leading to late detection and poor survival rates due to limited treatment options. PC can occur due to smoking, heavy drinking, chronic pancreatitis, obesity, diabetes, and poor diet choices. Family history, germline mutations (*BRCA 1/2*, PALB2), and syndromes like Hereditary Breast and Ovarian Cancer Syndrome (HBOC), Lynch Syndrome 2, and Peutz-Jeghers can also lead to PC.[9]

Genetic Association:

The following gene mutations are linked with pancreatic cancer: *KRAS, CDKN2A, TP53, SMAD4, BRCA1/2, STK11, PRSS1*, Lynch Syndrome, and *ATM*. The *KRAS* oncogene is found in about 90% cases as the most common mutation, and it aids in pancreatic cancer progression. *STK11* (Peutz-Jeghers syndrome) and *PRSS1* pose a high lifetime risk for pancreatic cancer patients. *ATM* and *BRCA1/2* are found in familial pancreatic syndromes and pose a moderate risk. *TP53* and *SMAD4* are mutated in most cases. *TP53* and *CDKN2A* interrupt the DNA's healing process, while *SMAD4* is an indicator of poor prognosis. Lynch Syndrome genes increase the risk of pancreatic cancer.[10] These gene mutations help initiate tumor progression and increase the risk of pancreatic cancer, so genetic testing is recommended for patients, especially for those who have a family history.[11]

Current Treatment Strategies:

Treatment options for PC include surgery, radiation therapy, chemotherapy, and immunotherapy. However, surgery is only possible for cancer that hasn't spread throughout the body. When considering surgery, the stage and cancer recurrence are reviewed. The four main stages of PC are resectable, borderline resectable, locally advanced, and metastatic. In resectable PCs, the tumor is fairly localized, making surgery possible. In borderline resectable and locally advanced PC, the tumor can be removed, but cancer cells that have spread remain. Surgery isn't possible in metastatic PCs due to widespread cancer. Besides surgery, treatment, and therapies can improve the quality of life.[12]

Surgery: The three main PC surgeries include the Whipple Procedure, Total Pancreatectomy, and Distal Pancreatectomy.[12] The Whipple Procedure removes the head of the pancreas, gallbladder, part of the bile duct, and duodenum. Distal Pancreatectomy removes the body and tail of the pancreas.[13] Total Pancreatectomy removes the entire pancreas.[12] A study at the Pakistan Kidney and Liver Institute (2018–2019) showed higher survival rates of the Whipple Procedure than the Distal Pancreatectomy, but with more complications such as delayed gastric emptying and pancreatic fistula.[13]

Radiation Therapy: Radiation therapy kills cancer cells through high-energy X-rays.[12] It can prevent the tumor from

growing by causing DNA damage and can be targeted to the affected area (local control). However, the benefits of radiotherapy alone are uncertain, and it does not improve overall survival. The old methods include 2D-radiation and the box technique. They work with large areas using low doses (40–60 Gy), lack precision, and have many side effects. A newer form of radiotherapy is Stereotactic Body Radiotherapy (SBRT). SBRT uses imaging for precision, high biologically effective doses (BED > 70 Gy), smaller fields, has survival outcomes of 14–20 months with little to no side effects, and provides local control. A study shows a 1-year survival rate of 96.4% and a 2-year survival rate of 70.8%. More trials are needed to confirm its effectiveness. 5-FU + Radiotherapy or Gemcitabine + Radiotherapy have an overall survival rate of 8–15 months.[14]

Chemotherapy: Chemotherapy prevents tumor growth using drugs that target various mechanisms/pathways of cell division and metabolism.[12] It kills cancer cells, prevents recurrence and tumor growth, and downstages the tumor for surgery. The most common types of chemotherapies are FOLFIRINOX, Gemcitabine, Gemcitabine + Nab-Paclitaxel, modified FOLFIRINOX, Gemcitabine + Capecitabine (GemCap), Nanoliposomal Irinotecan + 5-FU, and Olaparib. FOLFIRINOX is the strongest chemotherapy regimen that uses a combination of drugs (5-Fluorouracil, Folinic acid, Irinotecan, and Oxaliplatin) and has a survival rate of 11 months. Gemcitabine is weaker, with Gemcitabine + Nab-Paclitaxel providing a survival rate of 8.5 months. To prevent recurrence post-surgery, modified FOLFIRINOX is used, showing a 54-month survival rate. Chemotherapy helps slow disease progression, extend survival time, and improve quality of life, but it doesn't cure cancer.[15]

Immunotherapy: Immunotherapy helps the immune system fight cancer cells by activating T cells. In PDAC, the thick desmoplastic stroma, consisting of matrix collagen and fibronectin, does not allow immune cells to access the tumor microenvironment. PDAC is one of the immunologically 'coldest' tumors with high *PD-L1* expression and low MHC-I expression. This means that the tumor is highly resistant to immune-based therapies. With chemoradiation therapy or radiotherapy, PDAC can become a 'hot' tumor with high MHC-1 and low *PD-L1* expression. This allows T cells to recognize the cancer better and attack it. Thus, immunotherapy doesn't work on its own for PC, but combining it with chemoradiation or radiotherapy provides a better response.[16]

Current Treatment Outcomes:

After surgery, the median five-year survival rate increases to 20%–30%; however, there are high recurrence chances of 70%–80%, so neoadjuvant chemotherapy is given for borderline resectable and locally advanced patients before surgery (Table 1).[15]

Table 1: Comparison of pancreatic cancer treatments and their outcomes. Surgery provides the highest survival rate for resectable tumors, but the cancer has a high chance of recurring even after surgery. Neoadjuvant therapy can downstage borderline tumors, allowing for surgery, while chemotherapy, radiation therapy, and immunotherapy support maintenance of PC (created with data from[14-17]).

Treatment	Used For	Effectiveness	Notes
Surgery	Resectable pancreatic cancer	Five-year survival rate increases to 20%–30%	70%–80% recurrence even after surgery
Chemotherapy or Neoadjuvant therapy	Metastatic, Borderline, or Locally Advanced Pancreatic Cancer Controversial for Resectable pancreatic cancer	Downstage the tumor by 60%, making it applicable for surgery	Often given before surgery to reduce the tumor
Radiation therapy	Locally Advanced or Borderline Cancer	High-energy X-rays kill cancer cells	Average overall survival: 8.5 months
Immunotherapy	Recurring Cancer Borderline, Locally Advanced, or Metastatic pancreatic cancer	Fight the tumor using the T cell defense mechanism	Often combined with Chemoradiation or chemotherapy due to a weak immune response to pancreatic cancer

Other treatment modalities can include chemoradiation therapy and targeted therapy.[12] Targeted therapy attacks genes like *KRAS, BRCA1/2*, the RET gene, the NTRX gene, and the *BRAF V600E* gene. This form of therapy doesn't benefit alone but is often combined with other therapies. Using targeted therapy, specific genes are targeted, which could help reduce tumor microenvironment barriers.[18] Neoadjuvant therapy can downstage tumors by 60%, making surgery possible.[17]

However, it is important to consider that in most cases, combination treatment is used instead of using one of the treatment methods alone. As shown in the data from Table 1, the main treatment modalities have a low survival rate when used alone, so combining treatments improves results and overall survival. Chemotherapy, chemoradiation therapy, and radiotherapy are other treatments combined with surgery or immunotherapy. Although these treatment strategies provide various survival benefits, their effectiveness is strongly dependent on early diagnosis. Many of these treatments, especially surgery, are only possible during the early stages. When PC is detected late in the metastatic stage, treatment options become limited, leading to poor prognosis and survival rates. Thus, improving early detection is critical, as it may directly increase treatment options and overall treatment effectiveness.[19]

Standard Detection Methods:

MRI, EUS, CT scan:

Traditional imaging includes Magnetic Resonance Imaging (MRI), Endoscopic Ultrasonography (EUS), and Computed Tomography Scan (CT).[2] MRI scans can detect changes in the ducts often before they exist, without any harmful radiation, and they can differentiate between various soft tissues. However, they often cannot detect small, microscopic tumors. They take a long time to complete; thus, during the process, a person's breath can blur the picture or distort the image when the pancreas moves.[20] A study (2007–2020) from Onomichi General Hospital found that EUS detected 45.5% of stage 0 and 81.8% of stage I tumors, outperforming CT and MRI.

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EUS has a 94.4% sensitivity and can identify Main Pancreatic Duct (MPD) abnormalities; however, its accuracy depends on the operator's skill and often requires a biopsy afterwards.[21] CT is fast, available, and has good imaging due to its proximity. However, it uses radiation and can miss small tumors.[22] In conclusion, not all traditional imaging modalities use ionizing radiation, and in most cases, these imaging methods are unable to detect tumors or aren't sufficient for detection by themselves. Figure 2 shows that liquid biopsy is often able to detect the small tumors missed by the other imaging modalities.

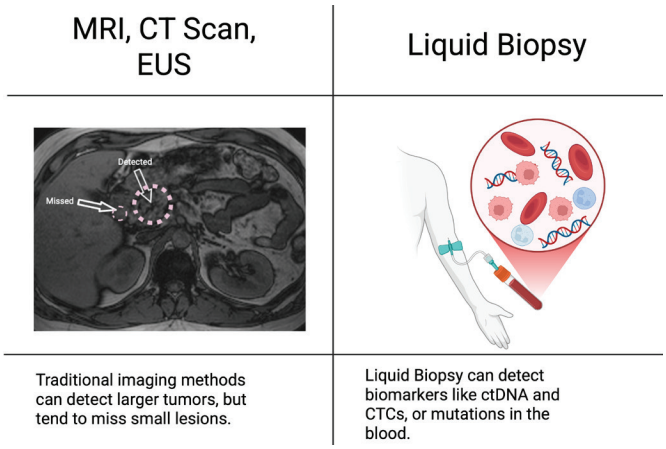

Figure 2: Schematic representation of diagnostic tools for pancreatic cancer. This illustration compares traditional detection methods with liquid biopsy. While traditional imaging methods like MRI, CT scan, and EUS detect larger tumors, liquid biopsy uses biomarkers like ctDNA, CTCs, and *KRAS* mutations to detect small lesions (Created using BioRender).

Finding cystic lesions like Intraductal Papillary Mucinous Neoplasm (IPMN), Mucinous Cystic Neoplasm (MCN), and Pancreatic Intraepithelial Neoplasia (PanIN) is another early detection method.[19] IPMN and MCN are easy to detect through imaging, unlike PanINs, which require surgery. These cysts are often discovered unintentionally, and they can develop into pancreatic cancer. However, many of the cysts don't turn into cancer and are harmless. Having different gene mutations like *KRAS* and *GNAS* for IPMN and MCN means that these lesions need to be examined during endoscopy. Many people get surgery for these cysts, which is often (in 78% cases) unnecessary.[23]

Biomarkers:

Biomarkers are proteins or DNA/RNA that indicate signs of a tumor at an early stage and show tumor progression. They can be used to detect cancer, determine the type of cancer, and monitor cancer prognosis. Circulating free DNA (cfDNA) is present in the bloodstream and is released from natural cellular processes such as apoptosis and necrosis. cfDNA originates from all cells in the body. However, in cancer patients, the tumor-derived fragments of cfDNA are known as ctDNA. These ctDNA fragments contain mutations like KRAS, TP53, and SMAD4, and the presence of these mutations distinguishes the ctDNA from the regular cfDNA by indicating that this is a tumor-derived fragment.[26] Common PC biomarkers include CTCs, ctDNA, *TP53*, SMAD4, *BRCA ½*, *CDKN2A*, CA-19-9, and *KRAS*, which may provide insights into the detection of PCs.[24] Liquid biopsy uses biomarkers to detect PCs. It uses body fluids to analyze ctDNA, CTCs, and other biomarkers. CTCs are actual cancer cells that float in the bloodstream, while ctDNA are bits of DNA that originate from the tumor. ctDNA and CTC cell analysis may determine detection, the cancer stage, recurrence, and survival outcomes.[25] Identifying biomarkers like Carbohydrate antigen 19-9 (CA19-9) and *KRAS* aids pancreatic cancer detection and monitors treatment. However, CA19-9 isn't native to PC, so it may be increased in patients who smoke or have inflammation.[26] The *KRAS* oncogene can be seen in many patients during the early stage of PC, aiding in early detection. Yet, there are low levels of the *KRAS* gene in the blood and cystic juice, most of which aren't specific to PC.[8] According to a recent study done on biomarkers, biomarkers like *MXRA8, LTBP2, PLA2G1B*, and *KIRREL2* have shown a specificity of 84% and a sensitivity of 95%, which is significantly better than CA 19-9 for PC detection.[24] Overall, these biomarkers could indicate the formation of PC, and detecting them early through liquid biopsy may improve the early detection of PC. To avoid false positive results, multiple biomarkers must be analyzed.

Novel Detection Methods:

Liquid Biopsies:

A non-invasive test, liquid biopsy utilizes body fluids to detect the Circulating Tumor Cells (CTCs) and Circulating Tumor DNA (ctDNA) fragments in the blood. Both provide a molecular analysis of the prognosis. They could be used for early detection, staging, recurrence, monitoring, and personalizing treatment.[25] Liquid biopsy aids in early detection because ctDNA may provide information on mutations or specific characteristics of the patient's tumor. ctDNA-based biopsies help differentiate between pancreatitis patients with the *KRAS* gene and between PDAC patients with the *KRAS* gene. However, there is a limited amount of ctDNA in the Circulating Free DNA (cfDNA), so ctDNA is often hard to detect.[26] An abundance of CTCs portrays an advanced stage of PC, which determines if chemotherapy should be given before surgery. Moreover, CTCs help provide information about disease stage and recurrence possibilities.[27] Staging is vital in determining treatment options for PC patients. CT scans and MRIs often can't detect molecular and microscopic details of the tumor, so a liquid biopsy is preferred for monitoring the tumor and its progression. Depending on the gene mutations present, treatment and the type of chemotherapy could be suggested to personalize treatment for the patient.[2] The noninvasive nature of liquid biopsy allows for continuous monitoring and for the test to be repeated easily through any bodily fluid (blood preferred). As shown in Figure 3, liquid biopsy detects ctDNA and CTCs using clinically applied bodily fluids like blood, stool, saliva, and urine to allow for early diagnosis, treatment monitoring, and improve survival rates.[5]

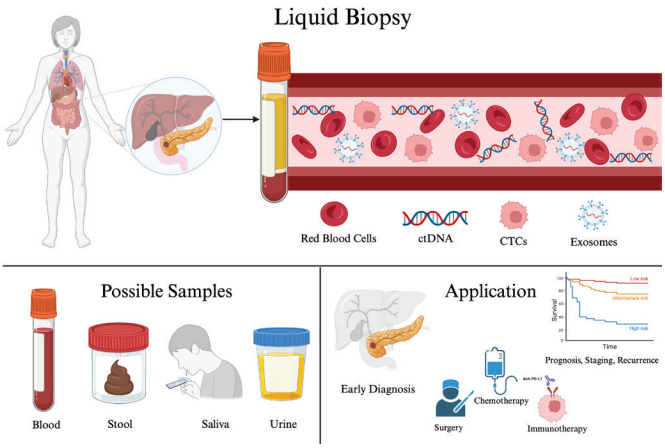

Figure 3: Liquid biopsy in pancreatic cancer. This illustration demonstrates liquid biopsy biomarkers, including ctDNA, CTCs, and exosomes, the bodily fluids that can be used during the biopsy, and the main clinical applications (Created using BioRender).

Breath Analysis:

Breath analysis for the diagnosis of pancreatic cancer and many other cancers is a fairly new concept. In the human breath are volatile organic compounds (VOCs) that are created by the body's metabolism. When diagnosed with PDAC or any cancer, the VOCs ratio changes. Acetone dimer and Dimethyl sulfide are two main VOCs associated with pancreatic cancer that increase if a tumor is present. Studies show that Acetone dimer was able to detect pancreatic cancer better than CA19-9 (0.91 vs. 0.796), and when Acetone dimer was combined with CA19-9 in detection, 96.7% sensitivity was shown. Breath analysis may open doors to easier non-invasive detection methods that have an increasing accuracy; however, research still needs to be done to provide assurance.[28]

Clinical Studies on Liquid Biopsy in Pancreatic Cancer:

The potential of liquid biopsy has been subject to several clinical trials, particularly analyzing Circulating Tumor DNA (ctDNA). *One such study is GUIDEMRD (Guiding Multi-Modal Therapies Against Minimal Residual Disease By Liquid Biopsies)* (NCT06102889), a clinical trial in Sweden that examines the relationship between positive ctDNA after surgery or chemotherapy and recurrence of PDAC via a liquid biopsy. Patients are required to provide a blood sample and must be scheduled for surgery. To prevent skewed results, the Electronic Health Record and the National Health Record are also checked. The aim is to test the role of post-surgery ctDNA in predicting survival rates, recurrence chances, and treatment options.[29]

In Germany, the *Prognostic Role of Circulating Tumor DNA in Resectable Pancreatic Cancer, or PROJECTION trial* (NCT04246203), investigates ctDNA to predict DFS and recurrence of RPC cancer post-surgery. Patients with RPC are monitored for 36 months or until death or cancer recurrence. A liquid biopsy will be done before surgery and 14 days post-surgery to monitor for ctDNA. The patients will be divided into two groups: Group A (with ctDNA present) and Group B (without ctDNA present). This study focuses on discovering the DFS for patients with RPC through the presence of ctDNA.[30]

Similarly, *Liquid Biopsy for ctDNA in Peritoneal Lavage and Blood in Pancreatic Cancer (LIPAC)* (NCT05400681) examines survival rates and the presence of *KRAS* mutations in peritoneal lavage fluid (PLF) or ctDNA. Having a *KRAS* mutation with positive PLF or positive ctDNA predicts poor prognosis and worse survival. Blood samples are collected before and after surgery to identify mutations and their relation to survival outcomes. Enrolled subjects must be at least 18 years old and PDAC patients with a pancreatic resection specimen. Therefore, the purpose is to portray the scope of liquid biopsy and check PLF and ctDNA for mutations to estimate survival rates.[31]

Pancreatic Cancer Initial Detection Via Liquid Biopsy (PANCAID) (NCT06283576), a study in Sweden, gathers results of the PANCAID blood test in early detection of PC, predicting recurrence, and tumor staging. IPMN lesions suggest the presence of cancer or the possibility of PC development. Enrolled subjects must be at least 18 years old and have a chance of increased IPMN levels. This blood test aids in the early detection of PC and recurrence rates, providing patients with the best possible treatment.[32]

Additionally, *Mutation of K-RAS, CDKN2A, SMAD4, and TP53 in Pancreatic Cancer: Role of Liquid Biopsy in Preoperative Diagnosis* (NCT03524677), in Ireland and Rome, analyzes gene mutations (*KRAS, CDKN2A, SMAD4, TP53, MET, EDIL3, BRCA1/2, RAB27A*) in blood samples to guide tumor staging and treatment options, and to predict cancer recurrence, prognosis, and surgery outcomes (DFS and OS). Before surgery, a blood sample from a group of 50 participants receiving pancreatectomy for non-metastatic PC will be collected. Patients must be 18 years or older and diagnosed with non-metastatic cancer to participate. Thus, this study focuses on the relationship between gene mutations and cancer results or prognosis.[33]

In France, *Liquid Biopsy and Pancreas Cancer: Detection of AXL(+) CTCs (CTC-AXL-PANC) (CTC-AXL-PANC)* (NCT05346536) compares the CellSearch and EPIDROP methods that detect AXL genes in ctDNA via liquid biopsy. AXL is a protein generally released by CTCs that correlates with a poor prognosis. To enroll in the study, patients must be 18 years old and have remote metastases with Pancreatic Cancer.[34]

South Korea's *Verification of Predictive Biomarkers for Pancreatic Cancer Treatment Using Multicenter Liquid Biopsy* (NCT04241367) investigates the *KRAS* gene in detection and prognosis estimation for PC patients via liquid biopsy. Enrolled patients must be pathologically confirmed with PDAC and must provide a blood sample. The droplet digital PCR (ddPCR) will examine the ctDNA for the *KRAS* gene and biomarkers. The study examines the correlation between the mutated gene and PDAC prognosis, cancer recurrence, response to treatment, or detection.[35]

Finally, Austria's *Liquid Biopsy (ctDNA) Guided Treatment in Localized Pancreatic Cancer: Neoadjuvant CTX vs. Upfront Surgery (LIQUIPANC)* (NCT06391892) tests the PFS and OS

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of LAPC patients after receiving chemotherapy before typical surgery. This novel pathway is chosen based on the liquid biopsy results through ctDNA analysis from a blood sample. Patients must be 18 years or older to participate. Overall, the study examines the effectiveness of their new strategy in improving the prognosis for LAPC patients.[36]

Collectively, these trials reflect the use of liquid biopsy in predicting quality of life, recurrence chances, staging, metastasis, and guiding treatment. All the trials utilized blood samples, gene mutations, and biomarkers to predict survival rates and aid in early detection and personalizing treatment. The following are common biomarkers and mutations used for detection and recurrence: CTCs, ctDNA, *KRAS*, CA 19-9, *BRCA ½*, *TP53*, SMAD4, and *CDKN2A*. Despite the diverse stages of pancreatic cancer studied—from resectable to metastatic—and varying sample types, these clinical trials collectively highlight the liquid biopsy's possible clinical potential in enhancing early detection, guiding treatment decisions, and improving prognosis. Results from these clinical studies, once completed, are likely to provide avenues for early detection and monitoring of prognosis to improve survival rates in this deadly disease (Table 2).

Table 2: Summary of clinical trials that employ liquid biopsy in the early detection and management of pancreatic cancer. These trials explore biomarkers like ctDNA, *KRAS*, and CTCs to predict recurrence rates, monitor tumors, early detection, and guide treatment options. Created using data from clinicaltrials.gov.

Clinical Trial ID #	Mutations & Biomarkers	Purpose	Samples
NCT06102889	ctDNA	Detect recurrence after treatment	Blood
NCT04246203	ctDNA	Predict recurrence & quality of life before and after surgery	Peripheral blood
NCT05400681	*KRAS*; *CDKN2A* *SMAD4*; *TP53* PLF+ctDNA	Correlate gene mutations in ctDNA and PLF with survival outcomes	Blood Peritoneal Lavage (PLF)
NCT06283576	*BRCA2* IPMNs	Use of the PANCAID blood test for recurrence, early detection, and development of PC	Blood
NCT03524677	ctDNA *KRAS*; *CDKN2A* *SMAD4*; *TP53* *MET* *BRCA1/2* *EDIL3* *RAB27A*	Predict staging, analyze tumors, and guide treatment in non-metastatic PC via liquid biopsy	Blood
NCT05346536	CTCs AXL	CTCs with AXL to predict recurrence, treatment effectiveness, and detection	Blood
NCT04241367	*KRAS* ctDNA *PD-L1*	Use *KRAS* gene biomarkers for detection and prognosis	Blood
NCT06391892	CA 19-9 *KRAS* ctDNA	Guide chemotherapy and predict survival in localized pancreatic cancer	Blood

Discussion

PC remains one of the deadliest cancers due to its late detection in the metastatic stage. Treatment methods like surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy are used to manage pancreatic cancer. Neoadjuvant therapy can be used to downstage the tumor to make it acceptable for surgery. Detection methods like MRI, EUS, and CT scan often miss small lesions that could indicate tumors at an early stage. Liquid biopsy may detect the small lesions that are often missed by standard detection methods. Its noninvasive nature allows for repeated use for tumor monitoring. Liquid biopsy may discover new gene mutations related to pancreatic cancer, and a variety of body fluids could be used. Overall, the use of liquid biopsy may improve the outcome, detection, and maintenance of pancreatic cancer and may potentially surpass imaging. Breath Analysis is another emerging novel method that may take early detection to a new level; however, further research and trials are required before it can be clinically applied.

Despite the various treatment and decision methods, pancreatic cancer survival rates and outcomes have not improved. This is mainly due to the following two reasons: 1) desmoplasia, 2) late detection when tumors are metastatic and unresectable. Current standard imaging detection methods (MRI, EUS, and CT scan) are inadequate to detect tumors at an early stage since they often miss small lesions. Liquid biopsy may detect small lesions and discover new gene mutations linked to pancreatic cancer, which may outperform imaging. It offers a noninvasive way to detect and monitor PC by detecting CTCs, ctDNA, or other biomarkers in blood and other body fluids, and its noninvasive nature avoids potential infections and allows for the test to be repeated multiple times. Since analysis of a few biomarkers could sometimes lead to false-positive or false-negative results, multiple biomarkers are analyzed to increase the accuracy of PC detection.[24] Thus, liquid biopsy may improve survival rates through its improved early detection and recurrence methods, and easy monitoring to check PC metastasis.

This review examined recent clinical trials on the application of liquid biopsy in detecting recurrence and monitoring pancreatic cancer. Although all trials were either ongoing or the results were not yet available, definitive conclusions could not be drawn, but some patterns emerged. Most studies showed that ctDNA analysis was used to personalize treatment, detect PC early, and predict recurrence. Blood samples were the most common method used in the majority of the studies. These studies mainly focused on early detection and recurrence. The biomarkers and mutations used included CTCs, ctDNA, *KRAS*, CA 19-9, *BRCA 1/2, TP53*, *SMAD4*, and *CDKN2A*. These trials highlight the potential of liquid biopsy in improving prognosis and survival through early detection and identification of recurrence rates.

Many studies examine the role of liquid biopsy in guiding treatment, predicting survival outcomes and recurrence rates, as well as facilitating early detection. Several trials analyze ctDNA through blood samples to help in early detection and estimating recurrence pre- or post-surgery. Analyzing the *KRAS* gene, ctDNA, PLF, and CTC-AXL may predict prognosis. The *GUIDEMRD* study and the *LIPAC* study examine ctDNA correlation with poor survival outcomes. Similarly, the (*CTC-AXL-PANC*) trial analyzes the relationship between positive AXL and survival outcomes. Thus, positive or high levels of biomarkers like ctDNA, PLF, CTC-AXL, and *KRAS* genes may indicate poor survival and prognosis. Multiple trials

have been using liquid biopsy analysis to estimate recurrence and guide treatment.

However, the potential outcomes of all the trials may not be the same. For example, some trials are conducted for different stages or types of pancreatic cancer, which include PDAC, non-metastatic, locally advanced pancreatic cancer (LAPC), and resectable pancreatic cancer (RPC). The variation in type or stages leads to varied results and outcomes. Moreover, there are a variety of biomarkers used. Some trials use multiple biomarkers and gene mutations, while others focus on *KRAS* or ctDNA analysis. The *LIPAC* clinical trial uses PLF and blood as samples to analyze. The rest of the trials only use blood samples to conduct research. Many of the trials use liquid biopsy as an additional factor to monitor treatment or predict recurrence. However, the *LIQUIPANC* study uses ctDNA to determine a treatment path that varies from the traditional path. This study performs chemotherapy before surgery based on ctDNA analysis from a liquid biopsy. Here, ctDNA analysis is used to diagnose and test a different approach to the treatment of PC. Varying study designs, cancer stages, and biomarker choices make it difficult to directly compare results. Moreover, as many trials don't have published results and are still ongoing, the outcomes aren't confirmed, limiting the ability to fully understand the effectiveness of liquid biopsy in clinical situations.

Overall, these studies demonstrate clinical application of liquid biopsy to improve prognosis, treatment strategies, early detection, recurrence prediction, OFS, DFS, and PFS. While some studies were conducted during different stages of PC and analyzed a different scope of biomarkers, some studies discovered a correlation between high ctDNA, PLF, CTC-AXL, and *KRAS* mutations and poor prognosis or survival. Analyzing multiple biomarkers helped guide treatment decisions, such as determining whether chemotherapy should be administered before or after surgery. These findings highlight the growing role of liquid biopsy in improving early detection, treatment planning, and monitoring of pancreatic cancer. However, ctDNA is normally low in early stages, which creates a detection challenge for liquid biopsy. Liquid biopsy is not directly compared to MRI or CT scans in these trials, and it is not widely used in real hospitals, as it is still a novel detection method. Combining liquid biopsy with imaging and AI could potentially improve detection rates and may provide more assurance of not missing the tumor during early stages. A combination approach may create a more cohesive and stronger detection method.

Future studies should explore the field of liquid biopsy in detail. Apart from CTCs and ctDNA, exosomes, extracellular vesicles, and microRNA, other biomarkers may play a role in improving early detection and monitoring of PC. Future trials should connect their study to all stages of pancreatic cancer and see which treatment approach fits best for which stage. Liquid biopsies may be combined with AI analysis in the future, and combination methods could be researched. For example, immunotherapy, chemotherapy, and radiotherapy may be evaluated, and their effects could be monitored through liquid biopsy.

Conclusion

This study examined the application of liquid biopsy in the diagnosis, treatment, and management of pancreatic cancer. Liquid biopsy provided significant potential for improved early detection, recurrence prediction, treatment guidance, survival outcomes, and tumor monitoring. ctDNA and CTCs analysis helped identify new biomarkers related to PC, like the KRAS gene. A biomarker amount or its sign (+ or -) could correlate with poor survival rates and prognosis. This is supported through the analysis of ongoing trials like LIPAC, GUIDEM-RD, and (CTC-AXL-PANC). The noninvasive nature of liquid biopsy allowed it to be repeated easily when required. However, a significant challenge remains at early stages, as ctDNA and CTCs may be insufficiently abundant for reliable detection, limiting diagnostic sensitivity. In the future, liquid biopsy could be combined with AI to enhance biomarker analysis and to identify new gene mutations. The use of other body samples for liquid biopsy and the use of breath analysis in the detection of PC could be explored further. In conclusion, liquid biopsy may enhance early detection, treatment, and management of pancreatic cancer through the analysis of ctDNA and CTCs.

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