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RESEARCH ARTICLE

CA19-9 as a Diagnostic Biomarker for Pancreatic Cancer

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Abstract

CA19-9 is a biomarker often used in pancreatic cancer diagnosis; it measures serum CA19-9 levels in the blood which corresponds to cancer status and even staging. It is used clinically but not as a screening biomarker as it doesn't have the specificity needed to make it cost-effective in a screening programme. It can be used before and after treatment as it can help in choosing a treatment plan. It is used to see if this treatment is working, so it works as a predictive and prognostic biomarker as well. It's recently been used alongside tumour marker genes to improve its sensitivity and specificity.

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Introduction

Pancreatic Cancer (PC) is serious medical condition with a low survival rate. In 2022, there were 62,210 new cases and 49,830 people died from it in the U.S. This shows there is a need for better ways to detect it early as patients do not find out they have it until it has already advanced, which makes treatment harder. People who are at higher risk, such as those with family history, smokers, older people, and those with diabetes, need better ways to be checked. If pancreatic cancer is diagnosed early, like at stage 1a, the survival rate can be as high as 68.7%, which is a better outcome.

Carbohydrate Antigen 19-9 (CA19-9) is one important biomarker that indicates how much cancer is in the body. While it is good for keeping track of treatment and understanding how a patient is responding to treatment, it is not specific enough for screening because it can show up in other health issues too. Moreover, around 5-10% of the patients do not make CA19-9, so the test might not work for everyone.

This paper investigates how CA19-9 helps with diagnosing and managing pancreatic cancer, what its limits are, and how using it with other markers might help detect the disease earlier. Understanding these issues is important to improve cancer treatment.

Pancreatic Cancer

Pancreatic Cancer (PC) is a highly fatal cancer; the 5-year survival rate is incredibly low. In 2022, incidence in the US was 62,210 and the number

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of deaths was 49,830 [1]. It has very poor prognosis and the main reason for this is that patients are often diagnosed at such a late stage [2]. Pancreatic cancer has been linked to smoking and diabetes and most cases occur in the elderly (60-80 years old). There are some gene mutations that are known to increase the chances of developing pancreatic cancer including BRCA2 and CDKN2A so there is a genetic predisposition in some patients [3]. About 10% of PC cases have familial basis; there is a much higher risk of developing cancer if one or more first-degree relatives have been diagnosed with PC [4].

Early detection of PC is of the utmost importance. A study of PC patients found that those diagnosed at stage 1a had a survival rate of 68.7% which is a promising prognosis [5]. As seen in figure 1, the survival rate of early-stage cancer is much better as treatment options like pancreatectomy are more effective before metastasis.

There is very clearly a need for a screening programme for people at risk of developing pancreatic cancer because early diagnosis greatly benefits prognosis of patients. This would include individuals with first-degree relatives with PC, smokers, the elderly, and people with diabetes. As of right now, the NHS doesn't have a screening programme for people at risk of developing pancreatic cancer.

CA19-9

Carbohydrate antigen 19-9 (also known as cancer antigen 19-9) is a biomarker that is a sign of abnormal glycosylation in pancreatic cancer. CA19-9 was first discovered as a biomarker in 1979 when it reacted with a 1116 NS 19-9 monoclonal antibody from a murine spleen inoculated with a human colon cancer cell line [6]. CA19-9 indicates circulating Sialyl-Lewis levels (a tetrasaccharide antigen) in the blood; tumours express more sialyl-Lewis antigens because it helps with extravasation and metastasis of the cancer [7]. The test is done by radioimmunoassay. The tests use specific antibodies and labelled antigens to find and quantify the select antigen (in this case, CA19-9) which form antigen-antibody complexes [8]. Raised CA19-9 levels in the blood (more than 36 u/ml) indicates a problem and will usually be followed by more tests. The test still works by CA19-9 reacting with a monoclonal antibody [9].

CA19-9 has proven to be an effective biomarker; in a study to test the sensitivity of CA19-9, the biomarker produced a result of 81.3% [2]. It has a reported median sensitivity of 79% and specificity of 82% [10]. It's important to note that this isn't just for late-stage PC. In a study of 726 phase II PC patients, CA19-9 had a sensitivity between 70-78% [11]. So, it can effectively detect early-stage PC as well.

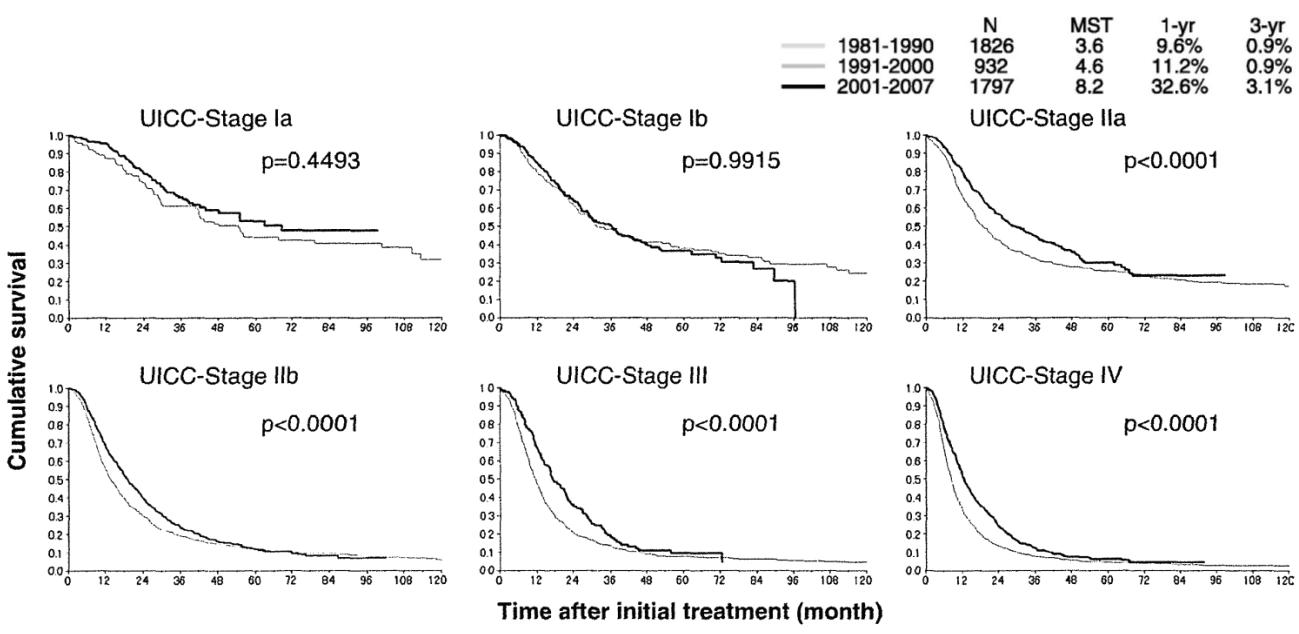

Figure 1 Graphs showing the 10-year survival of patients with pancreatic cancer after a pancreatectomy according to UICC stage. Stage I survival is high and significantly more promising than later stages. In stage II and onwards, the pancreatectomy made a statistical difference in survival rate. Egawa Shinichi, Japan Pancreatic Cancer Registry; 30th Year Anniversary, Pancreas 2012, figure 8 [5].

The problem with CA19-9 as a diagnostic biomarker for pancreatic cancer is that some pancreatic cancer cases have no Lewis antigen. About 5-10% of PC patients are Lewis antigen-negative meaning there will be very little CA19-9 in the blood [12]. So, for these patients a CA19-9 test would have very low sensitivity and would show as a false negative.

The perfect diagnostic biomarker would have perfect sensitivity and specificity; it would only detect the disease in question and not any other illnesses. Unfortunately, this is not CA19-9. There have been some cases of false positives where high CA19-9 levels are detected in patients with liver damage, inflammation, uncontrolled diabetes mellitus and some other non-pancreatic cancer pathologies [9]. This of course calls into question the specificity of CA19-9 and is part of the reason this biomarker isn't used to screen for PC.

Other biomarkers

While CA19-9 is still the only biomarker that has been FDA approved for pancreatic cancer, it's not the only biomarker that's been investigated in PC research. CEA (Carcino Embryonic Antigen) and CA125 levels are regularly tested and checked in PC patients and are followed throughout therapy to assess the tumour response to treatment. CA125 has been researched as a possible diagnostic biomarker for PC. While it's been found to be a fairly effective diagnostic biomarker of metastatic PC and non-invasive PC [13]. It is not as effective as CA19-9; it has a worse sensitivity and specificity and it definitely can't be used for screening as it detects many more pathologies than just pancreatic cancer [14]. It's mostly used in ovarian cancer patients.

While CEA has a much better specificity (89%), it unfortunately has very poor sensitivity (45%) [15]. It is mostly used as a predictive and prognostic biomarker.

However, these two biomarkers are not without their benefits; as seen in figure 2, where CA19-9 does a poor job of detecting PC in Lewis-negative patients, CA125 and CEA do a much better job [16].

Other uses of CA19-9 in PC

Because the CA19-9 test gives a quantitative result and the amount of CA19-9 in blood directly corresponds with the how far along the cancer is, CA19-9 can double as a prognostic biomarker. It can be used to help stage patients and give an accurate prognosis as patients with normal CA19-9 levels have a longer average survival than those with high CA19-9 in the blood [17].

CA19-9 is also sometimes used as a predictive biomarker. It's thought that when CA19-9 serum levels are below 100 U/ml the tumour can usually be removed in surgery (resectable) before it spreads but serum levels above 100 U/ml indicate a metastatic cancer [18]. However, there have been cases of lower [19] and higher [20] average CA19-9 serum levels for resectability of cancer in studies. It's used both pre- and post-operatively and in cases where the tumour isn't removed surgically CA19-9 can be used to monitor a patient's response to other treatment like chemotherapy. So it has been used as an effective prognostic and predictive biomarker in many studies and is used in treatment of patients (along with other biomarkers and tests) [21-23].

What's new for CA19-9?

In a study published last year, researchers found that considering fucosyltransferase (a tumour marker gene) genotypes in the interpretation of CA19-9 test results instead of applying a universal cut off point for the expected CA19-9 levels in PC patients can improve diagnostic accuracy [24]. Fucosyltransferase (FUT) genes are involved in the synthesis pathway of CA19-9. More specifically, the genes that code for the FUT2 and FUT3 enzymes have a great impact on CA19-9 secretion. The role of the FUT3 enzymes is to convert the CA19-9 precursor sialyl-Lewis, into CA19-9. FUT2 breaks it down and goes on to determine secretor status of ABO (blood group) antigens [25]. So, an active FUT3 enzyme, increases CA19-9 secretion, and an active FUT2 enzyme decreases CA19-9 levels in the blood. As a result, PC patients with FUT2 (aka Secretor) inactivity had increased CA19-9 secretion levels. Patients with lots of FUT3 (aka Lewis blood group) activity secreted a lot of CA19-9 and FUT3 inactivity meant minimal CA19-9 secretion [26]. So, as illustrated in figure 3, patients with FUT2 inactivity and FUT3 activity had high CA19-9 synthesis and secretion ability.

The way this study was carried out, was by separating patients into 4 groups based on their FUT genotype: FUT3-null (patients with 2 inactive FUT3 alleles), FUT-low (one inactive FUT3 allele and functional FUT2), FUT-intermediate (two active FUT3 alleles and functional FUT2) and FUT-high (two

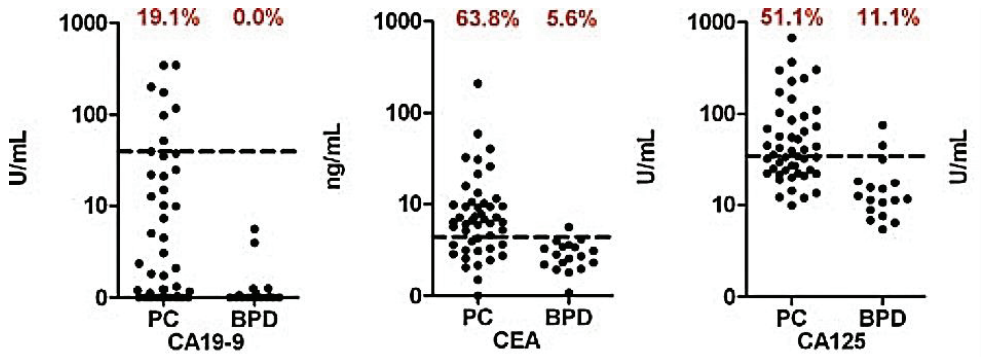

Figure 2 Graphs showing the sensitivity and distribution of CA19-9, CEA and CA125 in Pancreatic Cancer (PC) and Benign Pancreatic Disease Patients (BPD) with Lewis-negative antigen. CA19-9 has a low sensitivity to Lewis-negative antigen PC patients but CEA and CA125 have significantly better sensitivity. However their specificity is worse; they both detect more benign pancreatic disease cases.

Graph adapted from: Guopei Luo, Potential Biomarkers in Lewis Negative Patients with Pancreatic Cancer, Annals of Surgery, figure 1 [16].

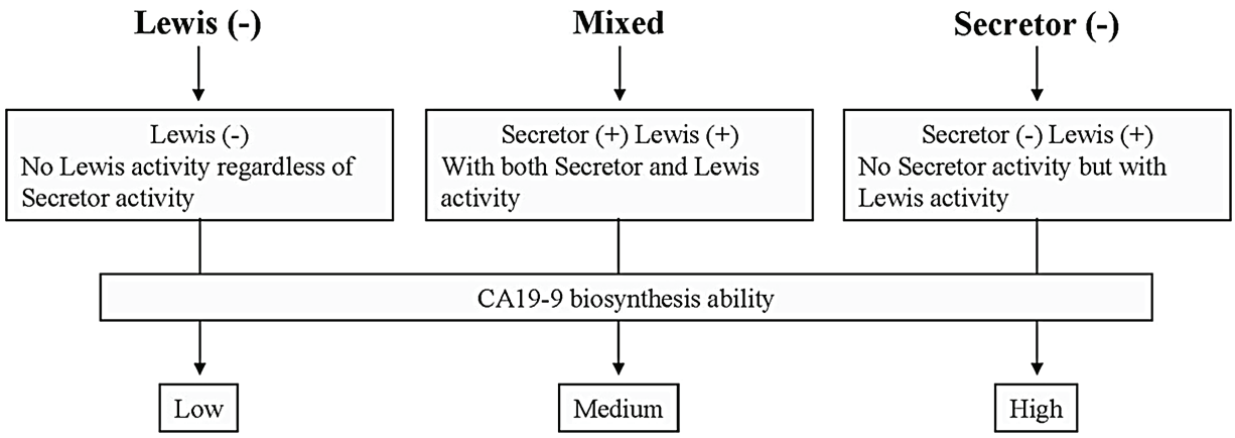

Figure 3 Diagram to explain how the combination of Secretor (FUT2) genotype and Lewis (FUT3) genotype both contribute to serum CA19-9 synthesis and secretion into the bloodstream. Negative Secretor and positive Lewis blood group genotypes both promote secretion of CA19-9 and raise serum CA19-9 levels in the blood. Guopei Luo, Optimize CA19-9 in detecting pancreatic cancer by Lewis and Secretor genotyping, Pancreatology, figure 1 [26].

active FUT3 alleles and inactive FUT2) using Next Generation or Sanger sequencing. Each genotype group is assigned its own diagnostic cutoff point based off of the CA19-9 secretion levels of each group and it provides better sensitivity and specificity results than the ordinary one-size-fits-all CA19-9 tests [24].

Conclusion

CA19-9 is a moderately accurate diagnostic biomarker of pancreatic cancer. It has a good sensitivity and specificity track record, but it's not perfect; it is not used to screen for pancreatic cancer because elevated CA19-9 serum levels are not unique to pancreatic cancer, so it doesn't have 100% specificity. It also rarely detects PC in patients that are Lewis antigen-negative, so it doesn't have perfect sensitivity either.

A recent study that proposed tailored cut off points for different FUT genotypes provided much better sensitivity and specificity results. This would massively improve the diagnosis rate of Lewis antigen-negative PC patients and lower the number of false-positives among FUT-high patients. These are promising discoveries in the world of CA19-9 as a diagnostic biomarker.

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