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Assessing the merits of existing pancreatic cancer biomarkers

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Pancreatic ductal adenocarcinoma (PDAC) suffers from a very poor prognosis because early stages of the disease are asymptomatic and thus diagnosis is delayed until late. Discovering a suitable PDAC biomarker could thereby improve PDAC treatment by having an early diagnosis. The carbohydrate antigen, CA 19-9, currently used for diagnostics, may help in assessing the disease stage, however it is unsuitable for screening purposes. PDAC specific nucleotides can be detected in plasma but not at the early stages of the cancer. Furthermore, measuring circulating tumour cells (CTCs) in patient blood entails high costs and is only useful for advanced stage disease. Other potential PDAC marker candidates are Laminin γ2A, Cyclophilin B and blood circulating adipokines, which seem to hold particular promise. At present, making early PDAC diagnosis is limited. The potential markers described herein might in the future be introduced into clinical practice however further studies are still required. Using combinations of several biomarkers also merit consideration, which may increase the overall sensitivity and specificity of PDAC detection.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) represents about 3% of all human malignant tumours [1]. It is one of those cancers occurring in highly developed countries, especially for men in their 70s and 80s. Over 20% cases are diagnosed when carcinogenesis is already at an advanced stage, including infiltration to adjacent organs or the presence of distant metastases. At the beginning of the disease, progression is asymptomatic whereas in late stage, the clinical picture becomes abruptly aggravated with symptoms depending on tumour localization, size and progression stage. When suspecting pancreatic cancer, ultrasonography is recommended, whose sensitivity is estimated to be at 80–90% [2]. Other medical tests applied are computed tomography and endoscopic retrograde cholangiopancreatography. Morbidity rates are very high; the five-year survival rate for radically treated patients being 3–18% [2]. Radical surgery is possible in only 20% cases due to the advanced stage of cancer upon diagnosis [3, 4]. The ability for detecting this cancer early could thus considerably improve its prognosis. Discovering a new biological marker may thereby accelerate the diagnosis and enable the delivery of appropriate treatment at an early disease stage. The presented work attempts to evaluate the utility of several potential pancreatic cancer markers (Tab. I).

CA 19-9, CA 125, CA 242, CEA

Carbohydrate antigens CA 19-9, CA 125 and CA 242 are often investigated and described, together with carcinoembryonic antigen (CEA), so that specificity and sensitivity may be improved when these biomarkers are jointly measured. CA 19-9 is a sialylated Lewis (a) antigen which is absent in 3–7% of the general population with a Lewis (a–b) blood-type antigen [5].

Amidst all the known PDAC markers, only CA 19-9 has been currently employed in diagnostics. Its sensitivity rate is 79% and specificity 82%, which limits its clinical value making it impossible to distinguish pancreatic cancer from benign pancreatic diseases and multiple carcinoma [6]. Because CA 19-9 is not tumour-specific protein, serum concentrations may also be elevated in patients with inflammatory diseases of the digestive tract and liver disease; particularly cholelithiasis [7].

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Table I. Clinical relevance of potential PDAC biomarkers

Potential screening markers	Potential monitoring markers
Nucleotides	CA 19-9
Adipokines	CA 125
Laminin 2a	CEA
Cyclophilin B	CA 242
	CTC

In the 1980s in Japan, an attempt to introduce CA 19-9 for screening purposes was made [8]. A study on 70,940 healthy individuals showed increased concentrations (> 37 U/mL) of the marker in 1063 cases (1.5%). There was no evidence of cancer in patients having concentrations of 37–100 U/mL whereas CA 19-9 levels were > 100 U/mL in 89 patients in whom 15 cancer cases (19%) were detected which included 4 instances of PDAC; two of these qualifying for radical surgery. This study thereby concluded that CA 19-9 as a PDAC screening marker was unsuitable. Nevertheless, CA 19-9 is the marker of choice when monitoring patients with ductal carcinoma of the pancreas [7]. High postoperative CA 19-9 levels have been associated with poor survival and may identify those patients who, as an alternative, should receive systemic therapy [6]. Dong et al. reported that a preoperative serum CA 19-9 concentration > 338.45 IU/mL may be a prognostic factor for poor prognosis [9]. According to Hartwig et al., postoperative CA 19-9 decreases are associated with longer survival whereas increased post-operative CA 19-9 might in addition be a prognostic factor for a poorer prognosis [3]. Some researchers suggest that postoperative CA 19-9 elevation is associated with a microscopic positive tumour margin and poorer survival as a consequence [10].

CA 19-9 could also be useful in monitoring the pharmacotherapy of PDAC. Boone et al. observed that a > 50% decrease in CA 19-9 levels is correlated with a longer survival of patients who underwent neoadjuvant therapy [11]; Tzeng et al. obtained similar outcomes [12]. Further studies are needed to confirm whether failure to normalise CA 19-9 levels could be an independent predictor of shorter survival.

CA 125 or MUC16 belong to the mucin family of glycoproteins [13] and is mostly known for detecting ovarian cancer [14]. To date, it has not been suggested for PDAC screening, nonetheless it may play a complementary role in PDAC diagnosis and prognosis besides that of CA 19-9 [15]. Chinese Study Group for Pancreatic Cancer considered CA 125 to be useful in the diagnosis and detection of metastasis, as well as in selecting the appropriate therapy and for monitoring disease progression, regression and recurrence [16, 17]. Interestingly, according to Luo et al. CA 125 is superior to CA 19-9 for predicting the resectability of pancreatic cancer where high levels may indicate an unresectable pancreatic cancer [18].

CEA (carcino-embryonic antigen) is glycoprotein involved in cell adhesion and has been used for diagnosing recurrent colorectal cancer [19] and it might also prove useful for detecting PDAC. As a single marker, CEA is of low sensitivity (30–88%) but when combined with others sensitivity may become increased [20].

CA 242 is also a tumour marker for sialylated Lewis carbohydrates that has been suggested for PDAC diagnosis. It appears to have the highest specificity when compared to CA 19-9, CA 125 and CEA but has a low sensitivity (67.8%), however it may improve the CA 19-9 discrimination rate [21–23].

A valuable study by Yu-Lei et al. jointly measured serum levels of CA 19-9, CEA, CA 125 and CA 242 in PDAC patients and achieved a higher detectability of 90.4% sensitivity and 93.8% specificity, than when markers were measured alone [21].

Nucleotides

MiRNA molecules are small single stranded RNAs consisting of 18–22 nucleotides, which modulate posttranscriptional expression of several genes. MiRNA deregulation may not only be associated with upregulation of genes involved in cancer progression (cell proliferation, migration and invasion), but also with apoptosis evasion, and chemoresistance [24]. A study by Xu et al. suggested that miR-486-5p allows the discrimination of patients between PDAC, chronic pancreatitis and normal subjects (AUC = 0.861) [25]. The study demonstrated that miR-938 is comparable to CA 19-9 when differentiating patients with PDAC from CP.

Because the miRNA profile consists of a panel of up--regulated or down-regulated miRNAs responsible for many of the aforementioned aspects of tumorigenesis, then evaluating this profile may provide a more sensitive and more specific method than measuring a single miRNA. For instance, miR-16 and miR-196a together with CA19-9, constitute an effective set of first stage tumour markers. Indeed, some workers believe that miRNAs may have a role in assessing a patient's prognosis and their selection for treatment [26]. As an example, upon measuring circulating non-coding RNAs (ncRNAs) in cases of advanced PDAC, useful information can be gained, such as predicting the patient's response to chemotherapy. Furthermore, Humeau et al. reported that PDAC-specific MiRNA can be detected in saliva samples [27] and indicate that MiR-23a and MiR-23b are both present in patients with intraductal papillary mucinous neoplasms; otherwise known as non-invasive PDAC precursors. Another suggested and promising PDAC biomarker is circulating cell-free DNA (cfDNA). This arose from the conception of a 'liquid biopsy', which consist of analysing pieces of nucleic acids from tumour cells in collected blood sample [28, 29]. CfDNA is derived from somatic DNA released into the systemic circulation following cellular necrosis and

apoptosis. Hadano et al. found that KRAS-mutated cfDNA was associated with significantly poorer survival in patients with resectable tumours [29] and it was suspected that the cfDNA tumour found may correlate with micrometastases, which are undetectable by imaging methods. This suggests that cfDNA-positive patients may be considered for any preoperative options such as neo-adjuvant chemotherapy. These outcomes have been confirmed by other studies [28, 30, 31]. Kisiel et al. detected PDAC hypermetylated DNA in pancreatic juice [32] and reported that such PDAC specific DNA-methylation markers may discriminate between early disease stage from normal tissue. Matsubayashi et al. likewise detected hypermethylated PDAC cfDNA in pancreatic juice [33]. In summary, both cfDNA and MiRNA should be therefore considered as potential PDAC screening markers. It is also worth mentioning that MiRNA can be isolated from the saliva, which is a non-invasive method allowing premalignant pancreatic lesions to become detected.

Circulating tumour cells (CTCs)

CTCs are tumour cells circulating in blood vessels with metastatic potential. They have been detected in patients suffering from breast, lung and prostate cancers [34]. Kulemann et al. found CTCs in 73% of PDAC patients (n = 11); with CTCs being found in patients at every stage of the disease [34]. Earl et al. measured CTCs in 20% of such cases (n = 35) [31] with six out of all seven patients with CTCs having metastases; one patient had a resectable tumour. These outcomes lead us to conclude that CTC may be a sensitive PDAC biomarker. In addition, PDAC is poorly vascularised and its invasion is often limited to the liver, and only involves other organs at very advanced stages [31, 35, 36].

Bissolati et al. investigated CTCs in portal blood collected during PDAC surgery [35] and showed no differences in survival rate between CTC-positive and CTC-negative patients. An increased risk of liver metastasis was however found in CTC-positive patients. It should be noted that CTC isolation is very expensive and we believe that it cannot be used as a screening biomarker but may be applied when monitoring PDAC progression.

Adipokines

Adiponcetin is a 244-aminoacids cell signalling peptide (cytokine) synthesised in adipocytes with serum concentrations being inversely proportional to the percentage of body fat [37]. Adiponectin plasma levels correlate inversely with cancer risk; especially those associated with obesity and insulin resistance. This cytokine has been suggested as a potent inhibitor of angiogenesis in vivo [38]. Other studies also indicate that, in vitro, it may inhibit endothelial cell migration and induce cell apoptosis via activation of caspases. Concentrations of plasma adiponectin is significantly higher in PDAC patients (24.95 mg/mL) compared to healthy (10.4mg/mL) patients and chronic pancreatitis cases (10.3 mg/mL) [37]; Chang et al. obtained similar results [39]. In contrast, Pezilli et al. observed no significant differences in adiponectin serum levels between controls and a PDAC group [40]. There is evidence that the adiponectin serum level is inversely proportional to PDAC risk [41]. Serum adipokine levels increase during the course of PDAC. Based on the aforementioned studies, adiponectin may thus become a future PDAC biomarker.

Another described adipokine, leptin, is a 167 aminoacid protein where its serum concentrations are proportional to the body fat mass [37]. Leptin is supposed to be a marker differentiating autoimmune pancreatitis patients from those with chronic pancreatitis (CP) and pancreatic cancer where significantly lower serum levels were measured in patients with CP and PDAC compared to autoimmune pancreatitis [40]; without any significant differences between CP and PDAC [40]. Sakamoto et. al also observed no differences in serum leptin concentrations between PDAC and CP groups [42]. In summary, adiponectin may play a part as a PDAC biomarker, whereas leptin has low significance in the diagnosis of this cancer.

Laminin

Laminins are high molecular weight glycoproteins contributing to basement membrane structure. They are made up of three polypeptide chains: the α, β and γ encoded collectively into 11 genetic variants [43]. The gamma chain emerges in three different genetic polymorphisms; one of which encodes subtype laminin gamma 2 (LAMC2) which has been suggested as a potential PDAC biomarker [44]. Kosanam et al. measured increased serum levels in PDAC patients (382.2 ng/mL) compared to those for benign tumours (140 ng/mL) and healthy individuals (87 ng/mL). LamC2 (AUC = 0.87) outperforms CA19-9 (AUC = 0.82) in differentiating between healthy and cancer patients. In contrast, CA19-9 is superior upon comparing benign and PDAC patients. The combined use of LAMC2 and CA19.9 could thereby permit a more effective discrimination between age-matched normal and benign patients from PDAC patients than the single marker measurement of CA 19.9 [44].

Cyclophilin B

Cyclophilins are group of proteins acting as molecular chaperones that fold, translocate and process newly synthesized proteins. Cyclophilin B (CypB) is a 21-kDa protein belonging to the cyclophilin family of peptidyl-prolyl *cis*--trans isomerases. By reversible modification of their protein structure, cyclophilins also serve as signalling switches, regulating the activities of transforming growth factor β receptor, epidermal growth factor receptor, tyrosine kinases and transcription factors such as c-Myb and interferon regulatory factor 4 [45]. Cyclophilins are widely expressed in the human body and highly conserved throughout evolution.

Increased expression of cyclophilin B was observed in stomach and breast cancers [46]. Ray et al. measured increased Cyp B serum levels in 24 patients with PDAC [47]. The mean CypB level was 295 ng/mL in the PDAC group and 60 ng/mL in the controls (n = 24). The authors believe that increased secretion of CypB into the bloodstream may be caused by oxidative stress in the hypoxic tumour environment.

Conclusion

At present, there are no tests available for confirming PDAC that are easy-to-perform, specific, sensitive, non-invasive and that are of prognostic value. Early detection and choosing appropriate treatment may significantly reduce mortality and increase survival time in patients suffering from pancreatic cancer. Although advanced methods such as computed tomography and ultrasonography are commonly used in medical practice, the mortality rate remains very high. The main reason is that diagnosis is made too late. Twenty percent cases are diagnosed at a very advanced stage and qualified only for surgical treatment. Thirty percent of such patients undergoing surgery are expected to relapse. The only appropriate marker available, CA 19-19, is however unsuitable for asymptomatic cases. At this time, hopes can be pinned on measuring adipokines as in the aforementioned instance of adiponectin and MiRNA profiles should also be considered as useful PDAC biomarkers. Measuring CTCs however is expensive and labour-intensive and therefore inappropriate for clinical practice. It is thus our opinion that a combination of measuring several biomarkers might increase the sensitivity and specificity of detection and allow such means to be introduced for the screening of PDAC.

Conflicts of interest: none declared

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