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REVIEW

Biomarkers in pancreatic adenocarcinoma: current perspectives

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Abstract: Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis, with a 5-year survival rate of 7.7%. Most patients are diagnosed at an advanced stage not amenable to potentially curative resection. A substantial portion of this review is dedicated to reviewing the current literature on carbohydrate antigen (CA 19-9), which is currently the only guideline-recommended biomarker for PDAC. It provides valuable prognostic information, can predict resectability, and is useful in decision making about neoadjuvant therapy. We also discuss carcinoembryonic antigen (CEA), CA 125, serum biomarker panels, circulating tumor cells, and cell-free nucleic acids. Although many biomarkers have now been studied in relation to PDAC, significant work still needs to be done to validate their usefulness in the early detection of PDAC and management of patients with PDAC.

Keywords: pancreatic cancer, biomarkers, screening, CA 19-9, CEA

Introduction

Despite making up only 3.1% of new cancer diagnoses, pancreatic ductal adenocarcinoma (PDAC) is currently the fourth leading cause of cancer-related death in the US, and has one of the worst outcomes of any malignancy, with a 5-year survival rate of 7.7%.[1] The National Cancer Institute estimates that 53,070 people will be diagnosed with pancreatic cancer and 41,780 patients will die of pancreatic cancer in 2016.[2] In contrast to most solid organ malignancies, in which there has been dramatic progress in recent years due to earlier diagnosis and targeted therapy, PDAC mortality rates are actually increasing.[1] It is projected that by 2030, pancreatic cancer will surpass breast, prostate, and colorectal cancers to become the second leading cause of cancer-related death, second only to lung cancer.[3] Although only 10%–20% of patients are diagnosed at a stage amenable to resection, surgery remains the only potentially curative treatment for PDAC. Over the last 25 years, there have been significant advances in patient selection, surgical techniques, and the perioperative care of patients with PDAC. As a result, the morbidity and mortality of pancreas surgery have declined considerably.[4–8] High-volume centers have reported 5-year survival rates as high as 27%.[9] For PDAC patients who undergo resection, the chances of further survival increase the longer the patients survive after resection, and a small subset of patients can experience long-term survival.[10] For example, a recent study using data from the National Cancer Database (NCDB) from 1998 to 2002 showed that 3.9% of patients with resected PDAC lived for 10 years after diagnosis.[11]

The only biomarker currently recommended for clinical use by the National Comprehensive Cancer Network (NCCN) guidelines for PDAC is carbohydrate antigen 19-9 (CA 19-9).[12] As such, a significant amount of this review is dedicated

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to review the available literature on the utility of this biomarker at several critical points in the clinical trajectory of PDAC patients with resectable disease. We discuss the sensitivity and specificity of CA 19-9, its ability to predict prognosis, and its utility in decision making about resectability and neoadjuvant therapy. We then discuss selected other serum antigen biomarkers as well as the potential role for panels of serum biomarkers which, when pooled together, can have much greater sensitivity and specificity than any single marker. We also discuss the case of human equilibrative nucleoside transporter 1 (hENT1) as an example of a mutation that could be used to guide targeted therapy. Finally, we discuss cell-free nucleic acid technologies and circulating tumor cells (CTCs). This review is not intended to be a comprehensive analysis of the multitude of biomarkers that have been evaluated for PDAC. Rather, it is intended to highlight the current clinical evidence for commonly used biomarkers, and to discuss technologies that we believe will be important in the coming years.

Carbohydrate antigen 19-9

CA 19-9, or sialyl Lewis antigen, is by far the most well-studied biomarker for PDAC, and the only one currently recommended for clinical use by the NCCN guidelines for PDAC.[12] It is recommended that CA 19-9 be checked preoperatively in all patients with suspected PDAC being considered for surgery and/or neoadjuvant therapy, after resection prior to adjuvant therapy, and every 3–6 months for 2 years postoperatively.[12] Despite this, national data suggest that CA 19-9 is only measured in ~25% of pancreas cancer patients.[13] CA 19-9 was first discovered in 1979 by using monoclonal antibodies in the serum of patients with advanced colorectal carcinoma, and later was found to be produced by pancreatic carcinoma.[14,15] A commercial assay was developed in 1983.[16] CA 19-9 has a number of mechanisms that may be involved in carcinogenesis. For example, induction of sialyl Lewis expression in cancer of digestive organs is accompanied by increased ability of cancer cells to adhere to endothelial cells through endothelial E-selectin.[17] However, CA 19-9 is also secreted by normal biliary epithelium, and can be markedly elevated because of benign biliary stricture, extra-pancreatic malignancies that cause biliary obstruction, biliary infection (ie, cholangitis), and inflammatory processes (ie, pancreatitis).[18,19] An important limitation of CA 19-9 is that ~10% of the population do not generate the specific sialyl antigen and are thus termed nonsecretors.[13,20,21]

Utility of CA 19-9 in screening in asymptomatic patients

Two large studies have evaluated CA 19-9 in screening asymptomatic patients for possible PDAC. A study in Korea screened 70,940 asymptomatic patients using CA 19-9 and abdominal ultrasound. Of 1,063 cases who had a CA 19-9 level above the upper limit of normal, only 4 patients had pancreatic cancer and 11 other malignancies were found.[22] The positive predictive value (PPV) was calculated at 0.9% in their asymptomatic population. A study in Japan screened 10,162 asymptomatic patients and found only 4 (0.4%) cases of PDAC.[23] Both of these studies concluded that screening asymptomatic individuals is not worthwhile for the early detection of PDAC.

Sensitivity and specificity of CA 19-9 for PDAC in patients being evaluated for possible PDAC

In 1990, Steinberg published a report summarizing 24 studies on the use of CA 19-9 in the diagnosis of PDAC.[24] This study reported on a total of 1,040 patients and 3,282 controls. The mean estimates for sensitivity and specificity were 81% and 90%, respectively, using an upper limit of normal level of 37–40 U/mL.[24] These sensitivity and specificity estimates have been often quoted in the literature since then. Notably, the controls in that study were healthy individuals without gastrointestinal complaints or known pancreatic abnormalities on imaging. In 2013, Poruk et al performed an updated meta-analysis to examine the sensitivity and specificity of CA 19-9 for PDAC using a control population of patients with known benign pancreatic disease.[25] A total of 57 studies containing 3,285 patients with pancreatic cancer satisfied the selection criteria for sensitivity calculations, and 37 studies including 1,882 patients with benign pancreatic disease satisfied the selection criteria for specificity calculations. The mean sensitivity was 78.2% (95% confidence interval [CI] 76.1%–80.2%), and the mean specificity was 82.8% (95% CI 79.9%–85.3%).[25] The sensitivity estimate was similar to that reported by Steinberg. The lower specificity estimate likely better reflects the actual clinical use of CA 19-9 in discriminating benign and malignant conditions in patients presenting with periampullary disease. As a primary screening test, CA 19-9 is convenient and inexpensive, but its lack of specificity results in a large number of false-positive examinations requiring further investigation, limiting its practical applicability.

CA 19-9 as predictor of resectability

Unresectable disease found only at laparotomy which was not detected by clinical staging remains a significant problem in PDAC. Such patients are subjected to the morbidity of a major surgery without deriving any therapeutic benefit. The reported negative predictive values (NPVs) of computed tomography (CT) for predicting resectability range from 88.2% to 100%, although most of these studies used older generation CT scanners.[26–29] A recent study reported on 256 patients in the era of modern thin-slice CT scanners reported that CT predicted the absence of metastatic disease in 85% of patients.[30] Several studies have examined whether CA 19-9 can augment imaging-based assessment of resectability.[31–35] As an example, Maithel et al reviewed a database of 491 patients who underwent staging laparoscopy before planned pancreatic resection for PDAC.[31] Median CA 19-9 was 131 U/mL for those who underwent resection versus 379 U/mL in those with unresectable disease (P=0.003). A receiver operator characteristic (ROC) curve was developed for CA 19-9 and resectability, and the statistically optimal cutoff was 130 U/mL. Unresectable disease was identified in 26% of those with CA 19-9 >100 U/mL but only in 11% of those with CA 19-9 <100 U/mL (P=0.003). CA 19-9 levels >130 U/mL remained a predictor of unresectability on multivariate analysis.[31] They suggested that CA 19-9 levels may allow surgeons to select patients for staging laparoscopy. Several other studies using a variety of cutoff points for CA 19-9 have shown similar findings.[32–35]

CA 19-9 as a predictor of prognosis

Numerous studies have demonstrated that elevated CA 19-9 levels are associated with worse stage-specific survival and recurrence.[13,36–38] Postoperative CA 19-9 levels are thought to be a more accurate estimate of prognosis than those obtained prior to resection.[36,37] Turrini et al showed that patients with elevated pretreatment CA 19-9 showed that patients with elevated pretreatment CA 19-9 whose CA 19-9 level normalized after surgery experienced comparable survival to those without pretreatment elevation.[36] Hata et al demonstrated that CA 19-9 levels that remain elevated postoperatively are associated with positive margin status and early hepatic- and peritoneal-based recurrence.[38] Sugiura et al performed an ROC analysis of CA 19-9 levels in 154 patients who underwent resection of PDAC.[39] They found that a CA 19-9 cutoff level of 100 U/mL was a significant predictor of recurrence within 6 months of surgery. Early recurrence occurred in 39 of 73 patients (53%) with CA 19-9 level >100 U/mL but in only 9 of 81 patients (11%) with a level <100 U/mL, and CA 19-9 remained a significant predictor of early recurrence on multivariate analysis (odds ratio [OR] 11.2).[39]

Several groups have examined the meaning of CA 19-9 level in patients treated with neoadjuvant therapy and patterns of response to neoadjuvant therapy. In a study from MD Anderson, Katz et al examined the ability of CA 19-9 level at time of diagnosis to predict successful completion of neoadjuvant therapy and surgical resection in patients with resectable disease.[40] They found that CA 19-9 levels >37 U/mL had a PPV for completing neoadjuvant therapy and resection of 86%, but the NPV was only 33%.[40] Patients with borderline resectable disease who experienced a decrease of CA 19-9 >50% during neoadjuvant therapy had higher odds or R0 margin status (OR 4.2, P=0.05).[40] Finally, a decrease in CA 19-9 during neoadjuvant therapy was associated with improved overall survival (OS).[40–42]

Patients with undetectable CA 19-9 levels (nonsecretors) have survival that is superior to CA 19-9 secretors overall, but have equivalent stage-specific survival compared to normal-level (<37 U/mL) secretors.[13,43] Brown et al evaluated the significance of CA 19-9 kinetics in an institutional database of 72 patients with at least 2 CA 19-9 levels planned for pancreatectomy.[44] ROC analysis revealed that an absolute CA 19-9 increase of ≥50 U/mL and a rate of increase of ≥1 U/mL per day identified patients who were unresectable on exploration. An absolute increase of <50 U/mL and a rate of increase of <1 U/mL per day predicted improved OS in the overall cohort, but not in patients who were able to undergo resection.[44]

Decision making about neoadjuvant therapy versus upfront surgery

The NCCN guidelines state that neoadjuvant therapy should be considered in selected patients who appear technically resectable but have poor prognostic features such as very elevated CA 19-9, large tumor size, large regional lymph nodes, excessive weight loss, or extreme pain.[12] A 2008 single-institution analysis of 143 patients failed to show cutoff level of CA 19-9 which would be useful to triage patients to neoadjuvant therapy, likely due to power issues.[45] Bergquist et al recently used the NCDB to formally evaluate the impact of CA 19-9 elevation at time of diagnosis in 10,806 patients with anatomically resectable early-stage (Stage I and II) disease.[13] They found that early-stage patients with CA 19-9 elevation had decreased survival at 1, 2, and 3 years (56% versus 68%, 30% versus 42%, and 15% versus 25%; all P<0.001) compared to those with normal levels.

Notably, CA 19-9 nonsecretors had equivalent survival to normal-level patients. This effect of elevated CA 19-9 on mortality hazard remained statistically significant after adjusting for confounders (hazard ratio [HR] 1.26, 95% CI 1.20–1.32). Neoadjuvant systemic chemotherapy followed by curative intent surgery was the only treatment that completely eliminated the survival disparity conferred by elevation of CA 19-9. The authors concluded that patients with elevated CA 19-9 at diagnosis should be considered "biologically borderline resectable" regardless of anatomic resectability based on imaging, and that neoadjuvant chemotherapy should be administered to all such patients.[13]

Carcinoembryonic antigen

Carcinoembryonic antigen (CEA) is the second most common serum biomarker currently used clinically to detect PDAC. Unlike CA 19-9, CEA is not recommended by the NCCN guidelines, although it is commonly obtained in clinical practice. The 2013 meta-analysis by Poruk et al estimated the mean sensitivity of CEA for detecting PDAC as 44.2% (95% CI 38.5%–50.0%) and the mean specificity as 87.5% (95% CI 82.5%–91.2%).[25] These findings are fairly similar to another recent review of 13 studies containing 1,323 cases, which reported a median sensitivity of 54% and a median specificity of 79%.[46] The fairly poor sensitivity in these studies indicates that CEA is inferior to CA 19-9 at identification of PDAC. However, the specificity is similar to CA 19-9, indicating that CEA performs well at identifying patients with benign disease. There is much less literature evaluating the prognostic impact of CEA compared to CA 19-9. Nonetheless, elevated CEA levels have been established as an independent predictor of decreased survival.[47,48]

CA 125

The utility of CA 19-9 is limited in patients with biliary obstruction, which elevates levels. CA 125 is a mucin-like transmembrane glycoprotein encoded by the *MUC16* gene which is overexpressed on the surface of ovarian cancer cells and is also secreted by other cancer cell types.[49,50] A recent study of 211 consecutive PDAC patients undergoing resection measured CA 19-9 and CA 125 within 14 days prior to surgery and evaluated them alongside other known prognostic factors.[50] High preoperative CA 125, higher stage, and lymph node status were independent predictors of OS and recurrence-free survival (RFS) in all patients, including those with elevated bilirubin. CA 19-9 was not predictive in those with elevated bilirubin, and there was no relationship between CA 125 and bilirubin levels. In patients with normal bilirubin, CA 19-9 was more predictive of OS and RFS than CA 125.[50] One study compared the utility of CA 125 in predicting resectability compared to 6 other biomarkers including CA 19-9.[51] CA 125 was found to have a superior predictive ability at predicting resectability compared to CA 19-9 and the other tested biomarkers.[51]

hENT1

Gemcitabine (GEM) is a pyrimidine nucleoside drug with efficacy against PDAC which is taken into cells by a nucleoside transporter.[52] hENT1 is a nucleoside transporter that may predict response to adjuvant GEM therapy. A retrospective study of tissue samples from the ESPAC-3 trial found that hENT1 expression predicted response to GEM but not 5-fluorouracil (5-FU).[53] Median survival for patients treated with GEM was 17.1 months for those with low hENT1 expression versus 26.2 months for those with high hENT1 expression (P=0.002). For the 5-FU group, median survival was 25.6 and 21.9 months for those with low and high hENT1 expression, respectively (P=0.36). hENT1 expression remained a significant predictor of survival on multivariate analysis.[53] Samples from the RTOG9704 trial were examined in a similar fashion, and hENT1 expression was associated with OS and disease-free survival in a multivariate model in the group given GEM but not the group given 5-FU.[54] Notably, both of these studies were performed using immunohistochemistry (IHC) with the 10D7G2 antibody. Retrospective analyses of the adjuvant and AIO-PK0104 CONKO-00 trials used a different antibody for the IHC analysis, and did not replicate these findings.[55,56] Unfortunately, the 10D7G2 antibody is currently not commercially available, and its utility would be limited to those cases for which tumor tissue is available for analysis. hENT1 is the main transporter of fluorothymidine (FLT), and it is possible that positron emission tomography imaging of FLT transport may act as a surrogate indicator for response to GEM. This possibility has been evaluated in vitro, but requires in vivo validation.[57]

Serum biomarker panels

As discussed in the section about CA 19-9, screening asymptomatic populations is problematic because of the potential for large numbers of false-positive examination. This same issue applies to a lesser extent in screening high-risk populations. Several studies have evaluated panels of biomarkers as a way of developing an overall test with a much higher sensitivity and specificity than that of any currently

available single biomarker.[58–61] Brand et al performed one of the largest studies of biomarkers to date by screening for expression of 83 serum biomarkers in 333 patients with PDAC, 114 patients with benign pancreatic conditions, and 227 healthy controls.[61] A cohort of 203 patients with breast, lung, or colon cancer was also included. They found that 42 of the 83 biomarkers differed significantly between PDAC patients and healthy and benign pancreatic disease controls. After splitting their cohort into validation and training sets, a Metropolis algorithm with Monte Carlo simulation was utilized to analyze all possible panels consisting of 2, 3, and 4 biomarkers. In their validation set, the panel of CA 19-9, intercellular adhesion molecule 1 (ICAM-1), and osteoprotegerin (OPG) demonstrated a sensitivity and a specificity of 78% and 94%, respectively, while the panel of CA 19-9, CEA, and tissue inhibitor of metalloproteinase-1 (TIMP-1) demonstrated a sensitivity and a specificity of 71% and 89%, respectively. The CA 19-9, ICAM-1, and OPG panel was selective for PDAC and did not recognize breast, lung, or colon cancers (all specificities ≥97%).[61] Similar results were seen by our group, which evaluated the panel of osteopontin, TIMP-1, and CA 19-9 achieving a sensitivity of 87%, a specificity of 91%, and an overall accuracy of 89.5%.[59] However, a follow-up to the Brand study utilizing pre-diagnostic serum samples from the Prostate, Lung, Colorectal, and Ovarian Screening Trial showed that the original panels were ineffective, perhaps illustrating a disadvantage of limiting panels to a minimal number of biomarkers.[62]

Firpo et al used a mathematical modeling approach to investigate the number of serum biomarkers that would be necessary to achieve a panel screen that could be practical in the general population, starting with the assumption that sensitivity would need to be ≥99% in order to raise the PPV to a clinically actionable level.[63] They started by identifying 9 biomarkers that are known to have elevated levels in PDAC patients compared to controls. They determined that a panel consisting of 40 biomarkers characterized individually by 32% sensitivity at 95% specificity would require any 7 biomarkers to be above the threshold and would result in a panel sensitivity of at least 99%.[63] A recent multicenter study utilized a 293-plex antibody microarray to identify protein profiles associated with PDAC in a sample of 156 patients with PDAC, 152 with other pancreatic disease, and 30 controls with non-pancreatic diseases.[64] They found that a biomarker signature could be identified using up to 10 biomarkers to differentiate PDAC from controls with >90% sensitivity and specificity. However, the implications of these findings on the utility of this approach for screening were limited because no healthy control subjects were evaluated, comparing instead to non-pancreatic disease controls.[64] More recently, the same group compared the signature of PDAC patients to healthy controls, and found similar results. Additionally, in this study, they found that accuracy of the signature increased with increasing stage.[65] For screening, of course, detection of the earliest stage (IA) pancreatic cancer, or the presence of high-grade dysplasia in pancreatic intraepithelial neoplasia or intraductal pancreatic mucinous neoplasm is the relevant goal.

We are not aware of any published experience with using serum biomarker panels to screen the general population or high-risk individuals. Although a complete discussion of the role of screening is beyond the scope of this review, it is generally agreed upon that screening the general population is not advisable or cost-effective, due to the low prevalence of PDAC. Efforts for screening need to be focused on those with >10-fold increased risk of PDAC, who account for ~10% of PDAC patients. One recently published study established that screening high-risk individuals can be successful.[66] Vasen et al performed a screening program consisting of yearly magnetic resonance imaging and possible endoscopic ultrasound for patients with familial pancreatic cancer (FPC) or gene defects known to predispose to PDAC. They found that surveillance of *CDKN2A* mutation carriers was relatively successful; PDAC was detected in 13 of 178 (7.3%) *CDKN2A* mutation carriers. Of these 13 *CDKN2A* mutation carriers who developed PDAC, the resection rate was 75% and the 5-year survival rate was 24%. The program was less clearly beneficial in FPC patients.[66] The success of this screening program for high-risk patients shows that screening programs can be successful at increasing detection at a resectable stage and improve survival. Although a multitude of biomarkers have been described in the context of PDAC in recent years, we are unaware of any published efforts of screening programs of high-risk patients which incorporate biomarker panels. A recent systematic review ranked the currently available PDAC biomarkers according to the Reporting Recommendation for tumor Marker Prognostic Studies (REMARK) scoring system.[67] These results should be used to develop biomarker panels that can be applied to screening patients at high risk of PDAC.

Cell-free nucleic acids

MicroRNAs

MicroRNAs (miRNAs) are endogenous noncoding RNAs of 19–25 nucleotides that negatively regulate gene expression posttranscriptionally by targeting mRNA for cleavage or

translational repression, and they are estimated to regulate over 60% of human genes.[68] miRNA dysregulation plays an important role in the cancer formation and progression, and miRNAs can act as tumor suppressors or oncogenes.[69] miRNA expression patterns are significantly altered in PDAC, and several studies have identified signatures associated with diagnosis, stage, progression, survival, and response to specific chemotherapy agents.[70–72] A recent study examined the ability of miRNAs to differentiate tissue from intraductal papillary mucinous neoplasms (IPMNs) and PDAC from controls.[73] The authors identified 607 miRNAs that were significantly dysregulated in PDAC and 396 in IPMN using next-generation sequencing. Of these, 40 miRNAs were commonly overexpressed in both. They validated their results in two other cohorts, including one with tissue obtained during endoscopic ultrasound fine-needle aspiration (EUS-FNA). They validated 30 miRNAs that were dysregulated in both PDAC and IPMN compared to controls. Importantly, their work shows that detecting these miRNAs in samples obtained from EUS-FNA is feasible, making these good biomarker candidates for early detection of PDAC.[73]

Cell-free DNA

Cell-free DNA (cfDNA) exists in the circulation as small DNA fragments. cfDNA is derived from DNA released into the bloodstream after cellular necrosis or apoptosis.[74] The detection of tumor-derived DNA in cfDNA, known as circulating tumor DNA (ctDNA), provides the opportunity to diagnose cancers and monitor chemotherapy-resistant mutations.[75] Hadano et al recently used droplet digital polymerase chain reaction to detect rare mutant tumor-derived *KRAS* genes in plasma cfDNA as ctDNA.[76] Of 105 patients undergoing pancreaticoduodenectomy for PDAC, ctDNA tumor-derived *KRAS* mutations were detected in 31%. OS was significantly poorer in patients with ctDNA (median OS 13.6 months versus 27.6 months, $P<0.001$). Presence of ctDNA remained a significant predictor of worse OS on multivariate analysis (HR 3.2, 95% CI 1.8–5.4).[76] Another study evaluated ctDNA *KRAS* mutations in 14 patients with advanced pancreatic cancer.[77] Ten (71%) patients had ctDNA prior to starting chemotherapy. Pre-therapy ctDNA level was a significant predictor of progression-free survival ($P=0.014$) and OS ($P=0.010$).[77] While absence of cfDNA in patients with confirmed PDAC seems likely to be clinically useful in predicting improved prognosis, the utility of cfDNA in early detection is likely to be limited by the relatively small proportion of patients with detectable levels.

Circulating tumor cells

CTCs are neoplastic cells shed into the bloodstream by a solid tumor.[78,79] CTCs are found frequently in the blood of patients with malignancies, but rarely in healthy controls, and are believed to be a source of distant metastases.[80,81] CTCs have been found in the blood of patients with all stages of PDAC, and their presence has been shown to be associated with poorer survival in several studies.[79,82–86] A recent study from Johns Hopkins Hospital evaluated blood samples from 50 patients with PDAC and tested for CTCs using immunofluorescence for cytokeratin, vimentin, and CD45.[87] Most studies of CTCs in PDAC have defined CTCs by the epithelial marker cytokeratin. The recent Johns Hopkins study characterized PDAC CTCs using both a mesenchymal marker (vimentin) and epithelial markers (cytokeratin positive, CD45 negative), which is relevant because the "epithelial-to-mesenchymal transition" is thought to facilitate metastasis.[88] The authors found cells with the epithelial phenotype (cytokeratin positive, CD45 negative) in 39 of 50 patients (78%). Of those, 26 patients (67%) had CTCs that were also vimentin positive, CD45 negative (the "mesenchymal-like" phenotype). On multivariate analysis, only presence of vimentin-positive CTCs was significantly associated with tumor recurrence (HR 2.78, 95% CI 1.31–5.88). However, the presence of cytokeratin-positive CTCs ($P<0.001$) but not mesenchymal-like CTCs ($P=0.39$) was associated with OS.[87]

While CTCs are not found in the blood of healthy controls, their presence is not definitive for PDAC. A recent study evaluated the significance of circulating epithelial cells (CECs) in 179 patients with pancreatic lesions.[89] CECs were identified in 49% of patients with PDAC, 64% of patients with neuroendocrine tumors, 62% of patients with IPMNs, and in 46% of patients with chronic pancreatitis ($P=0.41$). CECs were morphologically similar between patients with PDAC, and benign and premalignant lesions, and did not confer worse prognosis in those with PDAC.[89] The utility of using the presence of CTCs as a diagnostic tool is diminished by their rarity in PDAC; they are only found in 50% of cases, and are found even less often in early-stage cases.[90] Consensus on appropriate phenotypic markers, including cell surface antigens and cell size, in the context of circulating leukocytes is lacking. The use of CTCs for identification of molecular targets holds promise.

Conclusion

PDAC continues to have one of the worst overall outcomes of any solid organ malignancy, and there has been little

progress in recent years. There is currently an urgent need for validation of strategies using both novel and known biomarkers for early detection, diagnosis, prediction of prognosis, and stratification for different therapeutic approaches. CA 19-9 is useful for predicting prognosis and monitoring treatment. Patients with significant CA 19-9 elevation should be strongly considered for neoadjuvant therapy even if the tumor appears resectable on imaging. Those with elevated CA 19-9 preoperatively (regardless of whether neoadjuvant therapy was given) should be considered for staging laparoscopy prior to laparotomy. CEA elevations above the upper limit of normal are a poor prognostic sign. CA 125 should be considered for clinical decision making for patients who are nonsecretors of CA 19-9. Serum biomarker panels can achieve levels of sensitivity, specificity, and overall accuracy that are unlikely to be matched by any single biomarker. Strategies applying a blood-based biomarker panel to screen those at high risk of PDAC should be further investigated. miRNAs, cfDNAs, and CTCs are promising new technologies that are likely to play a major role in management of PDAC in coming years, but the utility of cfDNAs and CTCs is likely to be limited in screening and early detection by the small percent of patients who express these biomarkers. A multitude of biomarkers have been identified in PDAC in recent years. Prospective studies are needed to rigorously investigate the clinical impact of incorporating these biomarkers into clinical decision making in order to improve outcomes in this disease.

Disclosure

The authors report no conflicts of interest in this work.

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