ISSN 2664-8075 (Print) & ISSN 2706-5774 (Online)
South Asian Research Journal of Applied Medical Sciences
Abbreviated Key Title: South Asian Res J App Med Sci

| Volume-6 | Issue-3 | May-Jun- 2024 | **DOI: 10.36346/sarjams.2024.v06i03.006**

Review Article

Uptakes in Diagnosis of Carcinoma Pancreas

Dr. Anil Batta[1*]

[1]Professor & Head, Department of Biochemistry, Muzaffarnagar Medical College, Muzaffarnagar

***Corresponding Author:** Dr. Anil Batta
Professor & Head, Department of Biochemistry, Muzaffarnagar Medical College, Muzaffarnagar

Article History
Received: 03.05.2024
Accepted: 11.06.2024
Published: 12.06.2024

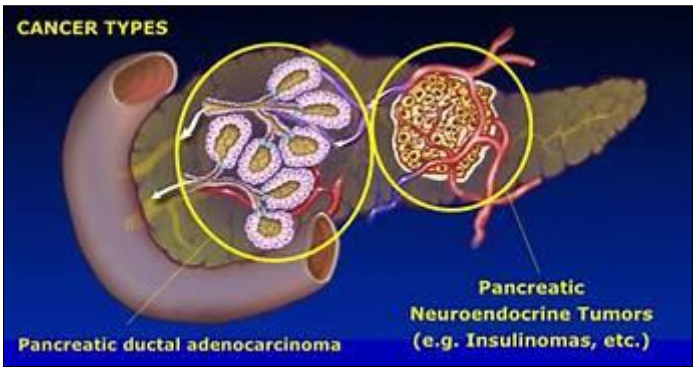
Abstract: Biomarkers play an essential role in the management of patients with invasive cancers. Pancreatic ductal adenocarcinoma (PDC) associated with poor prognosis due to advanced presentation and limited therapeutic options. This is further complicated by absence of validated screening and predictive biomarkers for early diagnosis and precision treatments respectively. There is emerging data on biomarkers in pancreatic cancer in past two decades. So far, the CA 19-9 remains the only approved biomarker for diagnosis and response assessment but limited by low sensitivity and specificity. In this article, we aim to review current and future biomarkers that has potential serve as critical tools for early diagnostic, predictive and prognostic indications in pancreatic cancer.

Keywords: Pancreatic Adenocarcinoma, CA 19-9, Future Biomarkers.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDC) is the most common subtype of pancreatic cancer, estimated around 85% [1]. Age-standardized incidence rate of PDC is 7.2 to 2.8 per 100,000 in developed region versus less developed countries [2]. In recent times, five years survival rate is minimally improved and reaches only 7% among all stages of pancreatic cancer [5]. The screening programs for PDC remains challenge compared with other tumors-lung, breast, colon and cervix. The barriers to develop screening test to detect pancreatic cancer include specificity of the chosen test and the relatively low incidence of the disease. This can lead to multiple false positive cases and further challenged by the cost and morbidity associated with invasive confirmatory testing. To overcome this in unselected patient population, a high performing screening test with sensitivity and specificity close to 100% is required. Current attempts to discover screening tests in PDC for early diagnosis have focused mainly on serum biomarkers. According to national cancer institute, the biomarker has been defined as any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or di The carbohydrate antigen (CA) 19-9, the only biomarker approved by US Food and Drug Administration (FDA) is not considered as a screening tool due to its low sensitivity and specificity [6, 7]. It was reported previously that the median sensitivity for CA19-9 was 79% while median specificity was 82% [8]. Therefore, the screening efforts were directed on the high-risk groups with familial risk and chronic pancreatitis; however, these represent the minority of affected individuals. In the sporadic pancreatic cancer group, no biomarkers so far with high enough accuracy are currently available for use in screening and therefore an urgent unmet need for identification of right biomarker [9]. The aim of this article was to review the novel biological and molecular biomarkers with diagnostic, predictive and prognostic potential in PDC patients.

Copyright © 2024 The Author(s): This is an open-access article distributed under the terms of the Creative Commons Attribution **4.0 International License (CC BY-NC 4.0)** which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited.



Diagnostic Markers

Most patients with early-stage PDC are asymptomatic, however commonly diagnosed at advanced stages, where the treatment options are limited and associated with worse clinical outcomes. The poor prognosis of PDC attributed to late diagnosis with advanced presentation, where curative therapeutic options are lacking. To date, there is no biomarker approved for early diagnosis. This underscores the unmet need for development of early detection biomarkers.

Carbohydrate Antigens and Carcinoembryonic Antigen

Serum carbohydrate antigen (CA) 19-9 is the most common and validated diagnostic tumor marker with sensitivity and specificity of 79-81% and 82-90% respectively; but have poor predictive value of 0.5-0.9% in asymptomatic patient [10]. CA 19-9 can be elevated in other medical conditions such as acute cholangitis, pancreatitis, obstructive jaundice and liver cirrhosis. Additionally, Lewis-negative blood type patient, which makes 5-10% Caucasian, do not produce CA 19-9 levels,10 thus contributing to false negativity. Currently, CA 19-9 is being applied in clinical practice for prediction of treatment response and prognostication. Few other carbohydrate antigens have also been studied extensively including CA-242, CA 50, CA 195, CA 72-4, CEA and CA-125, and found to be overall less sensitive than CA19-9 [11, 12].

MICRORNAS

MicroRNA (miRNAs) belongs to a class of non-coding RNA that involve in expression of post-transcriptional regulatory mechanisms. Use of miRNAs expression profiling has gained importance as a biomarker for early detection of cancer [13, 14]. In pancreatic cancer, miRNAs dysregulation has been profiled in pancreatic tissue, blood, stool and saliva [15]. Among several different miRNAs, miR-21, miR-155 and mi-R 196 have been demonstrated to be upregulated in PDC and can differentiate from pre-cancerous lesions as well [16-19]. Since specimen acquisition from pancreatic juice and pancreatic tissue, requires invasive approach, non-invasive techniques such as fecal and urinary specimen has been studied for diagnostic purposes. Three miRNAs (miR-143, miR-223 and miR-30e) as assessed in urine samples were over expressed in stage I cancer.

Macrophage Inhibitory Cytokine 1

Macrophage inhibitory cytokine 1 (MIC-1) is an autocrine regulatory molecule, which distantly belong to transformer growth factor beta (TGF-β) superfamily. Serum MIC-1 levels may serve as a novel diagnostic biomarker for early detection of pancreatic cancers. A study by Koopman *et al*., demonstrated that serum MIC-1 outperform all serum markers including CA 19-9 levels in distinguishing resectable pancreatic cancer from healthy controls. Recent studies including meta-analysis showed, serum MIC-1 levels were higher in pancreatic cancer patients as compared to controls.

GLYPICAN

Glypican 1 (GPC1), a membrane anchoring protein, found to be overexpressed in various cancers. GPC1 is highly expressed as assessed by immunohistochemical assessment, in pancreatic cancer tissue as compared to normal tissue. Additionally, GPC1 had an independent prognostic effect on overall survival. Similar results were reported for Glypican 3 (GPC3) in pancreatic cancers. A recent study by Yao *et al.*, reported overexpression of GPC3 associated with progression, carcinogenesis and poor progression in PDC. In a novel approach GPC1 circulating exosomes (GPC1 crExos) were monitored with flow cytometry in serum of patients and mice with cancer by Melo *et al*., GPC1 crExos demonstrated nearly perfect values when comparing patients with PDAC, chronic pancreatitis and healthy individuals.

Kras Mutation

KRAS mutations occur very frequently in pancreatic cancer and were extensively studied. The diagnostic accuracy of KRAS mutation was not optimal for diagnostic utility due to non-specificity of these mutations. The low level of cell-free circulating tumor DNA (ctDNA) in serum limits non- invasive assessments.

Osteopontin

(OPN), a protein of extra-cellular matrix, has been reported to be upregulated in pancreatic cancers with sensitivity of 80% and specificity of 97% for detection of pancreatic cancers.

Epigenetic Markers

Epigenetic changes can contribute to both cancer initiation and progression in PDC that evolves through non-invasive precursor pancreatic intraepithelial neoplasia. The Pans typically take 10 to 15 years to develop into malignant lesions that can further metastasize, thus an ideal context for the early detection. The serum markers, CA19-9 and radiological imaging are not reliable and therefore epigenetically silenced genes such as NTPX2, SARP2, RPRM, and LHX1 are currently under investigation. The sources for assessment of methylation markers include pancreatic juice, cell free tumor DNA and brush samples.

Predictive Biomarkers

The advanced pancreatic cancer patients associated with poor prognosis in spite of available therapeutic options it appears that overall emphasis in identifying predictive biomarkers is relatively low compared to diagnostic markers, likely due to limited therapeutic options. Gemcitabine markers.

Gemcitabine Biomakers

Gemcitabine, a nucleoside analog, since its approval in 1996 has been the cornerstone therapy for neo-adjuvant, adjuvant and palliative chemotherapy in pancreatic cancer. It was suggested that the two genes, GSTM1 and ONECU were found to be differentially methylated between responders and the non-responders.44 Cellular uptake mechanisms are the key to develop gemcitabine toxicity and resistance.

Folfirinox Markers

In metastatic pancreatic cancer, FOLFIRINOX (combination of folinic acid, 5-FU, irinotecan and oxaliplatin) reported to have survival advantage as compared to gemcitabine alone. Predictive biomarkers are essential for FOLFIRINOX therapy to avoid unfavourable side-effect profile. Higher tissue CES2 expression was correlated with longer OS and PFS who received neoadjuvant FOLFIRINOX treatment.

Nab-Paclitaxel Markers

In metastatic pancreatic cancers, combination therapy with albumin based nab-paclitaxel and gemcitabine reported significant improvement in OS and PFS compared to Gemcitabine alone. Glycoprotein osteonectin, also known as secreted protein acidic and rich in cysteine (SPARC), identified as a frequent site for aberrant methylation in pancreatic cancer. Several studies described the role of SPARC overexpression in pancreatic cancer and suggested its role in enhancement of paclitaxel delivery into the tumor as well.

Stromal Markers

PDC is quite unique because of extensive fibrosis that surrounds cancer cells, this fibrosis along with a poor blood supply has been found to limit delivery of drugs into cancer cells. A dense desmoplastic stroma surrounding the PDC can cause physical barrier to the delivery of chemotherapy and develop hypoxic tumor microenvironment that is immunosuppressive in nature. This is one mechanism by which pancreatic cancer is resistant to our current standard treatment. Hyaluronan is a major component of the extracellular matrix that comprises the stromal components of PDC and recently emerged as novel therapeutic target. Hyaluronidase is an enzyme that degrades this hyaluronan.

Brca Mutated Tumors

About 4-10% of pancreatic cancer patient are believed to have hereditary predisposition. Patients with familial history of pancreatic cancer, BRCA mutation prevalence can be up to 17%. Inactivation of BRCA1 and BRCA2, PALB2 a subset of tumors may predict response to platinum-based treatments (oxaliplatin, cisplatin and carboplatin). BRCA mutations are a potential predictive biomarker of response to PARP inhibitors and platinum-based chemotherapies. Superior overall survival was reported in stage III-IV pancreatic cancer patients having BRCA mutations treated with platinum (22-month vs non-platinum (9 months) chemotherapies. PARP inhibitors are pharmacologic inhibitor of poly (ADP-ribose) polymerase enzymes.

Microsatellite Instability

The reported incidence rate of microsatellite instability (MSI) in PDCs has been variable ranging from <5% to 13–17% of PDC patients. While outcomes from single agent immunotherapy trials in PC was disappointing, results from the pivotal KEYNOTE study revealed that pembrolizumab demonstrated 83% objective response rate (ORR) in the six evaluable pancreatic cancer patients suggesting that MSI status can predict the benefit from anti-PD-1/PD-L1 blockade C. It is recommended now to test all PCs for MSI status.

PD-1/PD-L1

Pancreatic cancers are typically deficient in T-cell infiltration which may explain the poor response to single agent immunotherapeutic. PD-L1 overexpression is associated with worse prognosis in a range of solid tumors, including PDAC.72 PD-L1 expression has been evaluated as a predictive biomarker for response to PD-1 inhibitors in other tumor types and was found to be correlated with better outcomes with PD-1/PD-L1 blockade.

Prognostic Markers

CA 19-9

Ca19-9 has also been studied for its prognostic value. Berardi *et al.*, reported high levels of Ca 19-9 independent unfavourable prognostic factor. Median overall survival if CA19-9 ≤37 U/mL vs >37 U/mL was 18.49 vs. 9.21 months respectively.

SMAD4

SMAD4 signal transformer from transforming growth factor beta (TGF-β), involves in pancreatic cells proliferation, apoptosis and serve as tumor suppressor gene. It was reported to be inactivated in more than 50% pancreatic cancer cases. Loss of SMAD4 expression was correlated with distant metastasis. The prognostic role is conflicting with few reports on worse prognosis with loss of SMAD3 expression while few other studies could not confirm those findings.

Angiogenesis Markers

Stromal cells in pancreatic cancer contribute in tumor progression by releasing angiogenesis factors such as platelet-derived growth factors (PDGF), matrix metalloproteinases (MMPs) and vascular endothelial growth factors (VEGF).

Inflammatory Markers

Cancer cells activate systemic inflammation pathways which anticipate tumor progression via complicated route involving cancer cell proliferation, inducing angiogenesis, evading growth suppressors and activation of metastasis.

Immune Markers

Several immune markers were investigated immunohistochemically (IHC) markers and correlated with prognosis. IHC markers associated with a worse prognosis include FOXP3, CD68, CD163, CD204, and CD66b;85 and the markers associated with an improved prognosis include CD3, CD8, CD4, CD20.86 High CD4+/CD8+ tumor infiltrating lymphocytes following curative resection was found to be an independent favourable prognostic factor for overall survival.

Micro Rna's

Besides its role as diagnostic biomarker, miRNAs, have been evaluated as potential prognostic marker. In a recent meta-analysis by Frampton *et al.*, demonstrated decreased OS and disease-free survival (DFS) in patients expressing high miR-21, miR-155 and miR-203; and low miR-34a levels.

SPARC

SPARC as discussed above as predictive biomarker for nabpaclitaxel, was evaluated for prognostication. SPARC overexpression in pancreatic cancer indicate poor outcome.96 Interestingly, SPARC overexpression in pancreatic cancer stromal cell demonstrated poor prognosis but its expression in tumor cells was not associated with prognosis.

Challenges in Biomarkers Studies

One of the major challenges in biomarker development is the collection of tumor tissue of adequate quality for analysis. Early diagnosis of PDC is usually performed with fine needle aspiration and therefore adequate tissue procurement is difficult to obtain. Pre-chemotherapy tumor biopsies frequently contain limited tumor cells (15%) or did not have ≥50% tumor content for high-quality tissue assessments. The failure in finding high-sensitive and high-specific biomarkers may also be attributed to the availability of relative fewer samples and lack of proper matching with cases and controls. It is also challenged by inadequate standard operating procedures in terms of sample collection, storage, analysis and interpretation of results.

CONCLUSIONS

A diverse array of novel biomarkers in terms of their diagnostic, predictive and prognostic potentials are currently being studied with the hope of finding effective management for this challenging cancer. Studies on innovative molecular markers such Glypican-1 and micro-RNA's, yielded encouraging results. The emerging immunomodulatory treatments for PDC present an opportunity for predictive biomarker development. Various combinations of these biomarkers demonstrated their potential use. However, the biomarker studies have been challenged by relatively low case numbers, absence of feasibility studies only, selection of early-stage samples and non-specificity of molecular markers. Nevertheless,

large studies with novel study designs are warranted to validate these biomarkers for clinical application. The optimal therapeutic management should be guided by the molecular composition of their tumor and these biomarkers play a crucial role in defining the way for precision treatment.

REFERENCES

1. Ryan, D. P., Hong, T. S., & Bardeesy, N. (2014). Pancreatic Adenocarcinoma. N Engl J Med, 371, 1039-4.
2. Simoes, P. K., Olson, S. H., Saldia, A., & Kurtz, R. C. (2017). Epidemiology of pancreatic adenocarcinoma. Chinese Clinical Oncology, 6(3), 24-24.
3. Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J., & Thun, M. J. (2009). Cancer statistics, 2009. CA: a cancer journal for clinicians, 59(4), 225-249.
4. American Cancer Society. What is pancreatic cancer?
5. Ferlay, J., Soerjomataram, I., & Dikshit, R. (2014). Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer, 136, E359-86.
6. Goonetilleke, K. S., & Siriwardena, A. K. (2007). Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. European Journal of Surgical Oncology (EJSO), 33(3), 266-270.
7. Gui, J. C., Yan, W. L., & Liu, X. D. (2013). CA19-9 and CA242 as tumor markers for the diagnosis of pancreatic cancer: a metanalysis. Clin Exp Med, 14, 225-33.
8. Goonetilleke, K. S., & Siriwardena, A. K. (2007). Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. European Journal of Surgical Oncology (EJSO), 33(3), 266-270.
9. Poruk, K. E., Firpo, M. A., Adler, D. G., & Mulvihill, S. J. (2013). Screening for pancreatic cancer: why, how, and who?. Annals of surgery, 257(1), 17-26.
10. Ballehaninna, U. K., & Chamberlain, R. S. (2012). The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence based appraisal. *Journal of gastrointestinal oncology*, *3*(2), 105-19.
11. Zhang, Y., Yang, J., Li, H., Wu, Y., Zhang, H., & Chen, W. (2015). Tumor markers CA19-9, CA242 and CEA in the diagnosis of pancreatic cancer: a meta-analysis. International journal of clinical and experimental medicine, 8(7), 11683.
12. Bünger, S., Laubert, T., Roblick, U. J., & Habermann, J. K. (2011). Serum biomarkers for improved diagnostic of pancreatic cancer: a current overview. Journal of cancer research and clinical oncology, 137, 375-389.
13. Lu, J., Getz, G., Miska, E. A., Alvarez-Saavedra, E., Lamb, J., Peck, D., ... & Golub, T. R. (2005). MicroRNA expression profiles classify human cancers. nature, 435(7043), 834-838.
14. Rosenfeld, N., Aharonov, R., Meiri, E., Rosenwald, S., Spector, Y., Zepeniuk, M., ... & Barshack, I. (2008). MicroRNAs accurately identify cancer tissue origin. Nature biotechnology, 26(4), 462-469.
15. Hernandez, Y. G., & Lucas, A. L. (2016). MicroRNA in pancreatic ductal adenocarcinoma and its precursor lesions. World journal of gastrointestinal oncology, 8(1), 18-29.
16. Bloomston, M., Frankel, W. L., Petrocca, F., Volinia, S., Alder, H., Hagan, J. P., ... & Croce, C. M. (2007). MicroRNA expression patterns to differentiate pancreatic adenocarcinoma from normal pancreas and chronic pancreatitis. *Jama*, *297*(17), 1901-1908.
17. Caponi, S., Funel, N., Frampton, A. E., Mosca, F., Santarpia, L., Van der Velde, A. G., ... & Giovannetti, E. (2013). The good, the bad and the ugly: a tale of miR-101, miR-21 and miR-155 in pancreatic intraductal papillary mucinous neoplasms. *Annals of oncology*, *24*(3), 734-741.
18. Szafranska, A., Davison, T. S., John, J., Cannon, T., Sipos, B., Maghnouj, A., ... & Hahn, S. A. (2007). MicroRNA expression alterations are linked to tumorigenesis and non-neoplastic processes in pancreatic ductal adenocarcinoma. Oncogene, 26(30), 4442-4452.
19. Tang, S., Bonaroti, J., Unlu, S., Liang, X., Tang, D., Zeh, H. J., & Lotze, M. T. (2013). Sweating the small stuff: microRNAs and genetic changes define pancreatic cancer. Pancreas, 42(5), 740-759.
20. Debernardi, S., Massat, N. J., Radon, T. P., Sangaralingam, A., Banissi, A., Ennis, D. P., ... & Crnogorac-Jurcevic, T. (2015). Noninvasive urinary miRNA biomarkers for early detection of pancreatic adenocarcinoma. *American journal of cancer research*, *5*(11), 3455.
21. Yang, J. Y., Sun, Y. W., Liu, D. J., Zhang, J. F., Li, J., & Hua, R. (2014). MicroRNAs in stool samples as potential screening biomarkers for pancreatic ductal adenocarcinoma cancer. *American journal of cancer research*, *4*(6), 663.