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Review Article

Improving and Standardization in Diagnosis of Pancreatic Cancer

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ABSTRACT

Most cases of pancreatic cancer is lately diagnosed, the commonest reason behind remains diagnostic configuration and deficient in sign and symptoms. Long term survival of pancreatic cancer leans on a solid procedure for diagnosis which leads to concrete impact regaining a successful treatment. As known the current mortality of pancreatic cancer is very close to the incidence. In recent years, progression have been made in diagnosis along with advancement of investigating modalities monitoring and screening of high risk group conversant with exploring wide range of non-invasive tumor markers. Among several strategies, molecular technology has been introduced in diagnosing and prognosis of pancreatic cancer. Lately pancreatic cancer initiation and prognosis including cell cycle, apoptosis, DNA repair, invasivity and metastasis seems to be associated with certain miRNAs. The process may involve positive or negative regulation of expression of proto-oncogenesis and tumor suppressor genes diverse miRNA are expressed abundantly at different level among normal pancreatic tissue, chronic pancreatitis and pancreatic cancer. Hence miRNA serve as tools in differentiating chronic pancreatitis from early stage of cancer. The expectation is high following the early diagnosis of pancreatic cancer. This article is to review the diagnostic framework to build-up the early diagnosis and aimed early treatment of pancreatic cancer.

KEYWORDS: Diagnosis**,** microRNA, Pancreatic cancer.

INTRODUCTION

Pancreatic cancer (PC) is the 4th most common cause of cancer related death worldwide. 5yrs survival rate is still <5% despite aggressive multidisciplinary treatment and the median survival is 5-8 months.[1] Recent surgical technologies, preoperative management and varieties of investigations have bit improved the conditions of the disease. Development of effective therapies, improvement in survival depends on early diagnosis and treatment modalities based on individual patient characteristics. Therefore early detection of PC is essential to get the satisfied result in curing the disease. However, lack of early diagnosis along with local invasiveness and distant organ metastasis is the prime factor resulting the disease more complicated with poor prognosis.[2] Risk factors with broad factorial involvement are seen in pancreatic cancer. Familial cancer syndrome and genetic morphological changes have leaded the disease to spread vigorously. Other increased risks of PC are those with breast cancer with fault BRCA2.[3] PC also may developed in case of familial adenomatous polyposis (FAP)[4] and hereditary non polyposis colorectal cancer.[5]

SCREENING FOR PANCREATIC CANCER: ENDOSCOPY AND ULTRASONOGRAPHY PROCEDURE

a.Endoscopic Retrograde Cholangiopancreatography (ERCP): In Pancreatic malignancies both biliary and pancreatic-duct strictures usually occurs ie ‘‘double-duct sign’’.[6] ERCP was a gold standard for cystic lesions of the pancreas, and evaluation of biliary strictures or a "double duct sign".[7] ERCP biopsy and brush cytology are norms that obtains tissue for diagnosis. However the sensitivity rate for ERCP-directed brush cytology or biopsy is very low.[8] Techniques to enhance the accuracy of brush cytology, e.g. The technique like digital image analysis, appear to be significantly increased to yield the brush cytology.[9] The management of patients with unspecified pancreaticobiliary stricture is a question because of the low sensitivity of current ERCP-guided tissue sampling methods. As finding a proper technique probe-based confocal laser endomicroscopy (pCLE) provides microscopic visualization of strictures along with an ongoing ERCP.[10] The significantly higher accuracy of ERCP and pCLE as compared with ERCP with tissue acquisition, due to its reliable microscopic

examination and its excellent sensitivity and negative predictive value, pCLE is highlighted as modern procedure.[11]

b. Intraductal Ultrasonography and pancreatoscopy: Pancreatoscopy along with intraductal ultrasonography (IDUS) is used in recent scenario because of its magnificent and reliable diagnostic evaluation instead the single procedure and results shows prominent improvement in differential diagnosis between malignant and benign intraductal papillary mucinous tumor (IPMT).The cumulative survival rate and disease free survival rate are increased by 95% and 93% respectively.[12] Pancreatoscopy provide the direct image of ductal structures as a result pancreatic adenocarcinoma remarkably get differentiated from intraductal papillary mucinous neoplasm and other cystic neoplasm.[13,14] whereas IDUS exhibit the nature of ductal strictures either benign or malignant.[15]

c. Abdominal ultrasound (AUS): AUS represents the minimal invasive and low cost scanning technique easily accessible for monitoring and evaluation of obstructive jaundice and biliary obstruction It may also reveal obvious metastases in liver. Thus, AUS can slightly visualize pancreas in an inadequate fashion, because the deep pancreatic bed and overlapping gas filled stomach or loops of bowel reduced the amplitude of ultrasound. The result differs hand to hand since it has proportionately low sensitivity for spotting small neoplasms within the head of pancreas.[16] So, overcoming the limitations new techniques like color power Doppler ultrasonography, ultrasonographic angiography, contrast harmonic imaging and three-dimensional ultrasonography has led to discover the new level of diagnosis improving the sensitivity and specificity of Ultrasonography.[17,18]

d. Endoscopic ultrasound guided Fine Niddle Aspiration (EUS-FNA): EUS-FNA is widely used in certain circumstances like unresectable pancreatic solid mass. It has a high accurate diagnosis in small mass comparatively with computed tomography (CT) guided FNA.[19] Though it has low predictive value but has relatively high diagnostic accuracy. Because of this drawback it is not recommended in potentially resectable pancreatic tumor however in unresectable pancreatic tumor EUS-FNA is appreciated in need of pathological diagnosis to switch on to neo-adjuvant or palliative radio/chemotherapy. EUS-FNA is a solution to obtain a sample of primary pancreatic lesion or possible metastases which are unsuspected with other imaging modalities.[20] Chen et al. demonstrated that EUS was superior to CT and was equivalent to MRI for tumour detection and T and N staging of ampullary tumors.[21]

IMAGING MODALITY FOR PANCREATIC SCREENING

a. Computed tomography (CT): Multi-Phase CT scanning has improved the diagnostic capability and has tremendous efforts in providing high imaging values with more sensitivity and specificity in cancer studies over the past few decades.[22,23] CT scan is strongly recommended as the primary modality for evaluating patients with suspected malignant biliary obstruction, detection of liver metastases, invasion of vascular structure, potential lymph node involvement including pancreatic neoplasm both for diagnosing and staging.[24,25] Multidetector computed tomography (MDCT) has improved the accuracy in diagnosis and evaluation of respectability degree of pancreatic neoplasm along with pancreatic parenchymal and peri-pancreatic vascular involvement.[26] Based on MDCT, the number of surgery has been doubled with refined techniques combined with new advanced chemo and radiotherapy,[27] Neverthless CT and MRI had a low sensitivity (71%) and specificity (58%) in intermediate disease stage ie borderline resectable disease predicting vascular involvement and resectability in the post-chemotherapy.[28]

b. Magnetic Resonance Imaging (MRI): Multi MR-imaging techniques has be evolved a revolution and considered as investigation of choice for diagnosing pancreatic neoplasm.[27] Long established MR-imaging yielded high accuracy and less false diagnosis for staging and evaluating pancreatic carcinoma. However, its sensitivity and specificity is still low as compared to CT.[8] Gradually to obtain the good result modified technique like Magnetic resonance cholangiopancreatography (MRCP) and Magnetic resonance angiography (MRA) has been discovered. This novel discovery has improved the values of diagnosis and differentiating the degree of staging in pancreatic neoplasm.[25] MRCP has elucidate the height and cause of obstruction with strong reliability than CT, recognizing difference between cystic versus solid lesions and also provides excellent ductal imaging, the only drawback is less sensitive in calcified lesions.[30] Unenhanced and contrast-enhanced MRI with MRCP and MRA has deliberated considerable remarks in patients suspecting pancreatic tumor.[25]

c. Positron emission tomography (PET) scan: PET-scan has been an investigating modalities of pancreatic cancer in recent days.[32] It is proved that F-Fluorodeoxyglucose (FDG) has greater affinity in adenomas which helps to differentiate the nature of the disease.[33] FDG-PET scan is more reliable in pancreatic adenomas rather than pancreatic cancer.[34] Similarly in chronic pancreatitis, FDG uptake is lower because of inflammation. However, FDG has excessive avid with salivary gland and suggest that the probability of autoimmune pancreatitis and assumed to recognize pancreatic cancer along with chronic pancreatitis.[35] PET-scan is considered as better evaluating tools as compared with EUS providing the pooled sensitivity of 90.1% and 81.2% respectively.[36] Similarly PET-scan detecting pancreatic cancer has noted the sensitivity of 90% and

95%and specificity of 82% and 100% in similar literature review.[37,38] For pancreatic cancer staging PET-scan has shown similar result as CT and proves that PET-scan has no beneficial effects in recognizing local tumor and regional lymph node spread.[39] Similar molecular based imaging 3-deoxy-3 [18F] fluorodeoxyglucose is also in use for differentiating pancreatic cancer. The utility of Flurothymidine-PET (FLT-PET) is narrow in abdominal imaging because of high hepatic uptake[40] even though some studies demonstrate that FLT-PET is more specific than FDG-PET however the result is vice versa in sensitivity test.[41] The improvement of sensitivity in initial staging of pancreatic cancer has been found by combining FDG-PET along with CT.[42]

LAPAROSCOPIC STAGING AND LAPAROSCOPIC ULTRASONOGRAPHY

The aim of laproscopic and laproscopic ultrasonography in pancreatic and peri ampullary cancer is sensible to detect the missed occult metastatic lesion in liver and peritoneal cavity where imaging modalities fails to detect the micro lodgement of neoplasms well as neoadjuvant chemo therapy can also be started early because of its reduced invasiveness.[43] In case of doubtful MDCT, laproscopic ultrasonography is the investigation of choice and have good approach of detection.[44] The use of this procedure helps to refine the case of unresectable carcinoma accompanying with an improvement in resection rate.[45]

FECAL DNA AND RNA SCREENING

Blood based markers has been used to approach the noninvasive procedure for distinguishing different cancers, Beside many research had recommended that alteration of genetic and epigenetic changes in RNA and DNA plays a vital role in early detection of cancers and potentially detected in feces in gastrointestinal related cancers.[46] Secreted pancreatic juice (1.5L/day) flow via bowel and finally excreted in faeces. This fact reflects that molecular changes can also be observed in faecal specimen. As a result faecal biomarkers has been encouraged either for detection of molecular changes in DNA and RNA sequel or simply DNA and RNA Therefore, it has high probability in early detection of Pancreatic cancer.[47]

PANCREATIC JUICE SCREENING

It has been used as alternative biomarkers in early prediction of pancreatic cancer. The several mutation in DNA is observed in the duodenal collection of secretin stimulated pancreatic juice.[48] This strongly prove that the sample are high quality source that can find a molecular changes in DNA and RNA regarding pancreatic cancer.[49] Similarly Masao Tanaka et al. reported that twisted expression of RNA in pancreatic juice were hugely degraded into fragments shorter that 200 nucleotides and helps to distinguish pancreatic cancer with non-invasive neoplasm.[50] As a result this might improve the early diagnosis and help in upgrading surveillance of patients in pancreatic cancer.

SERUM (BLOOD) TEST FOR THE DETECTION OF PANCREATIC CANCER

Till date there is no commercially recommended food and drug administration (FDA) approved blood test for pancreatic cancer. The majority of blood markers include carcino embryogenic antigen (CEA) and carbohydrate antigens along with majority of protein markers identified by mass spectrometry analysis. New wide range of identification values had raised with detection of molecular changes ie genetic and epigenetic markers (mRNA, DNA, microRNA).[51,52] The parallel comparison is challenging because of diverse population. As a result wide range of sensitivity and specificity were reported for the various markers. A.K. Siriwardena et al. in a literature review reported, pooled data from 2283 patients evaluated carbohydrate antigen CA19-9, the median sensitivity is 79%(70%-90%) and median specificity 82%(68%-91%) however, specificity of non malignant jaundice in response of CA19-9 is less considerable.[53] At present circumstances systematic sample collection, processing and storage should be taken in consideration from large screened population to yield reliable outcomes in early diagnosis of various cancers including pancreatic cancer.

micro RNA

Micro RNAs comprise a novel endogeneous non-coding RNA fragments (22 neuclotide) that plays key role in regulation of gene expression by directing their target mRNA for degradation or translational repression. First microRNA is initially discovered in 1993 by Victor Ambros' in 1993 in Caenorhabditis elegans.[54] Since then, different mRNA were identified in plants animals and humans. Till the time the updated database listed 2555 humans miRNAs has been explored and most of them are aberrantly expressed in various malignancies.[55] At present date when we go through human MicroRNAs, disregulation of miRNA are reported in multiple case of cancer and have revealed the clear involvement in disease findings and progression.

miRNA- DYSREGULATION IN TUMORS AND BLOOD SAMPLES

Numerous research groups has compared the status of miRNA in normal pancreatic tissues and pancreatic cancer to analyse the aberrant expression of miRNA similarly large numbers of miRNAs in serum or plasma are reported to be significantly raised and followed by diagnosis of the pancreatic cancer. The several miRNAs are involved and responsible for the transformation of cancers in pancreatic cells. miRNA-21 possess oncogenic effects which are over expressed that increases the proliferation and frequency of cell division in pancreatic cancer.[56] Similarly, miRNA-221 and

miRNA-192 equally falls on oncogenic genera, over expressed in pancreatic cancer that vulnerably increases the cell cycle progression.[57] In total evaluation of 29 studies, that reported the status of miRNA in tissue and blood of pancreatic cells are miRNA-21in10 studies,[59,62-67,70,71] miRNA-155 in 7 studies,[63,65,68-70,79,80] miRNA-196a in 12 studies.[51,58-60,64,67-69,76,79-80], miRNA-221in 3 studies[61,68,82] and miRNA-222 in 5 studies,[60,69,71,80,81] The respective studies showed the aberrant changes in miRNAs. These miRNAs are implicated in development of tumor in pancreatic cells. miRNA-155 has been recently identified as a candidate biomarkers in pancreatic neoplasm. Likewise miRNA-196a has shown the parallel progression of the diseases. The four miRNAs: miRNA-21, miRNA-210, miRNA-155 and miRNA-196a possesses a sensitivity of 64% and specificity of 89%.[65] Similarly miRNA-16 and miRNA-196a dominate the independent role in diagnosis of pancreatic cancer, however; these miRNA-16 and miRNA-196a along with combination of CA-19-9 delivered the sensitivity of 92% and specificity of 95.6%.[51] This combination reflects obvious increment in sensitivity and specificity in diagnosis of pancreatic cancer. The evidence strongly supports the facts behind diagnostic characteristics of miRNA in pancreatic cancer.

DISCUSSION

In recent years, large range of evidence has gathered regarding systematisation of clinical investigation related to pancreatic cancer. Some of the investigation has revealed expectations in improving the quality of diagnosis. This review has considered possible available research to generate accuracy in diagnosis of pancreatic cancer. Regardless ERCP – guided brush cytology is standard investigation in pancreatic cancer however, the significance is limited so pCLE (probe-based confocal laser endomicroscopy) is more reliable as modern procedure. Similarly, pancreatoscopy along with intraductal US (IDUS) carries an important role to manifest the nature of ductal strictures to rule out benign or malignant. Plain abdominal ultrasound is not reliable nevertheless Doppler ultrasonography or ultrasonographic angiogram contrast, harmonic imaging and three dimensional ultrasonography has confounding expectation in diagnosis of pancreatic cancer. In case of unresectable pancreatic solid mass FUS-FNA has high accuracy compared to CT. Imaging and occupies broad circumference in diagnosing various solid masses. CT, MDCT, MRI and PET-Scan has improved the accuracy in the field of diagnosis in pancreatic cancer Laparoscopic ultrasonagraphy boost to detect the microlodgement of neoplasm and clears the criteria in resection of carcinoma. Since the recent discovery the role of DNA and microRNA in cellular activity is being observed very closely. The ideas and knowledge on their activities has endeavoured to improvise the technique regarding various carcinomas in the last decade. The divergent physiological process linked with initiation and development of various solid and nonsolid cancers, we have been able to establish the role of miRNA in diagnosing and progression of the disease. Several miRNA like miRNA-21, miRNA155, miRNA-196a, miRNA-221, miRNA-222 are either tumor suppressor or oncogenic molecules respectively, have been illustrated and being identified their role in early detection, prognosis and suitable therapy of the patients. Likewise combination of miRNA-16 and miRNA196a along with CA-19-9 has shown the tremendous result in early diagnosis of pancreatic cancer. We are more optimistic in the indication of miRNA research promising for the use of diagnosing and delivering the personalized medicine to introspect the overall treatment outcome and survival of pancreatic cancer. The success of miRNA seems to have intensed result ever before. The focus should be more determined concerning miRNA in coming future.

ABBREVIATIONS

PC, Pancreatic cancer; FAP, Familial adenomatous polyposis; ERCP, Endoscopic retrograde cholangiopancreatography; pCLE, probe based confocal laser endomicroscopy; IDUS,.Intraductal ultrasonography; IPMT, Intraductal papillary mucinous tumor; EUS-FNA, Endoscopic ultrasound guided fine niddle aspiration; EUS, Endoscopic ultrasonography; CT, Computed tomography; MDCT, Multidetector computed tomography; MRI, Magnetic resonance imaging; MRCP, Magnetic resonance cholangiopancreatography; MRA, Magnetic resonance angiography; PET-Scan, Positron emission tomography scan; FDG, Flurodeoxyglucose; FDG-PET, flurodeocyglucose positron emission tomography; FLT-PET, Flurothymidine positron emission tomography; RNA, Ribonucleic acid; mRNA, messanger RNA; miRNA, microRNA; DNA, Deoxyribonucleic acid; FDA, Food and drug administration; CEA, Carcinoembryonic antigen; CA19-9, Carbohydrate antigen 19-9.

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