



Pancreatic Cancer: Early Detection and Surveillance



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Abstract

Pancreatic cancer (PC) is characterized by extremely high mortality and poor prognosis. Unfortunately, compared with other malignancies, there has been little improvement in the survival rate of patients with PC in recent decades. In almost all cases, pancreatic cancer is detected in the non-resectable advanced stages because the disease is usually asymptomatic in the early stages. At the time of diagnosis 20% of patients have localized disease, approximately 30% present with regional disease, and more than 50% present with distant disease. The only cure pancreaticoduodenectomy, is available to fewer than 20% of patients. Moreover, chemotherapy and immunotherapy regimens have limited efficacy in patient with nonresectable disease [1]. Since therapeutic choices are limited at the advanced stage, screening and early diagnostic tools are indispensable for a better prognosis. This article reviews current screening methods used in high risk patients and discusses some of the methods in development to improve early detection.

keywords: Pancreatic Cancer; Screening; Endoscopic Ultrasound; Biomarkers; Magnetic Resonance Imaging

High Risk Population

Although most cases of pancreatic adenocarcinomas are thought to be sporadic, up to 10% may be due to an underlying genetic predisposition. "Familial pancreatic cancer" (FPC) has been used to describe families with at least 2 first-degree relatives (FDR) with pancreatic cancer without a known genetic defect. Aggregation of pancreatic cancer in these families is due to an unidentified, autosomal dominantly inherited gene with reduced penetrance. A population-based, case control study conducted in the United States found that individuals with a first-degree relative (FDR) with pancreatic cancer had a 3.2-fold increased risk of developing pancreatic cancer [2] as compared to population controls. Hemminki et al. [3] also demonstrated 1.7-fold increased risk of pancreatic adenocarcinoma in an individual with a parent with pancreatic cancer [3]. The risk of pancreatic cancer based upon family history can be determined using a Mendelian risk assessment tool which calculates the probability that an individual carries a deleterious mutation in a pancreatic susceptibility gene.

Current Screening Methods

Appropriate combination of biomarkers and imaging technologies greatly improves the accuracy of early diagnosis.

Current Biomarkers

Cancer Antigen 19-9

This cancer antigen 19-9 (CA 19-9), a sialylated Lewis blood group antigen has been the standard serum tumor marker utilized

for diagnosis, prognosis, and recurrence detection in patients with pancreatic cancer. However only 65% of patients with resectable PC have elevated serum CA19-9 levels [and elevated level of CA19-9 has been observed in other gastrointestinal malignancies, such as gastric cancer and colorectal cancer, and in various benign conditions, including chronic pancreatitis and acute cholangitis Therefore, recent efforts have been focused on improving the diagnostic efficacy of CA19-9 by combining it with a panel of markers[4].

Carcinoembryonic Antigen Carcinoembryonic antigen (CEA)

CEA is the second most common serum biomarker used in clinical practice for pancreatic cancer diagnosis. It has sensitivity of 54% and a specificity of 79% for discriminating between malignant and benign conditions [5]. However, CEA is less accurate than CA 19-9 for malignant pancreatic cancer diagnosis.

Serum Glucose

Recently, new-onset diabetes has been recognized as an early manifestation of pancreatic cancer, which could aid the diagnosis of asymptomatic patients with pancreatic cancer. Identification of new-onset diabetes could lead to diagnosis at an early resectable stage, as early as 18 to 24 months [6]. However, several studies have shown either no association or mild increased risk for pancreatic cancer in patients with long-standing diabetes. In one

of the studies approximately 1% of diabetes subjects aged ≥ 50 years will be diagnosed with pancreatic cancer within 3 years of first meeting criteria for diabetes.

Amylase and Lipase

Pancreatic enzymes such as amylase and lipase represent another group of tumor marker used for pancreatic cancer diagnosis and follow-up. The enzymes lack enough sensitivity and specificity

Current Imaging Methods

Imaging methods currently used for pancreatic cancer screening include CT, MRI, and magnetic resonance cholangiopancreatography (MRCP).

Computed Tomography

It is generally known that the smaller the tumor size and the earlier the clinical stage, the better the prognosis. Small pancreatic cancer is defined as a tumor smaller than 2 cm with or without invasion to the peripancreatic vasculature or metastasis. Contrast-enhanced helical CT has facilitated the detection and staging of pancreatic cancer and is accepted as one of the most effective imaging techniques for the diagnosis of pancreatic cancer. The main early signs detected in the CT scans are pancreatic ductal dilation and CT has a threshold for lesion detection of 0.3 to 0.5 cm.

Gangi and colleagues conducted a study, 2 radiologists blindly interpreted 62 CT scans performed before a pancreatic cancer clinical diagnosis was made, and both radiologists agreed that suspicious findings were present in 50% of CT scans performed within 18 months prior to pancreatic cancer diagnosis and only in 7% of CT scans performed more than 18 months. Maximal pancreatic enhancement and optimal enhancement of peripancreatic vessels is essential for the detection of pancreatic carcinoma. Pancreatic-phase imaging (40–70 s after infusion of IV contrast material at 3 ml s⁻¹) is important for the detection of pancreatic tumor and evaluation of peripancreatic vasculature involvement. Lu et al. [7] explained that, compared with hepatic-phase imaging, pancreatic-phase acquisition provides significantly better pancreatic, arterial and portal venous enhancement with improved tumor–pancreatic contrast.

MRI and Magnetic Resonance Cholangiopancreatography MRI

MRI with MRCP allows more successful tumor detection at an early stage than multi-detector CT. However, small or non-contour-deforming pancreatic adenocarcinomas may lack classic imaging features and thus may not be detected on conventional MRI [8]. The use of functional imaging methods such as diffusion-weighted imaging may allow earlier detection of pancreatic adenocarcinoma [9].

Pancreatic cancer is usually hypointense in T1-weighted images compared to the pancreatic parenchyma. A study comparing MRI with CT scans showed no significant differences, with similar sensitivities of 84% and 86%, respectively. MRCP imaging is superior to CT scans or MRI in distinguishing inflammatory, nonmalignant pancreatic masses from pancreatic cancer [10].

Endoscopic Screening

Endoscopic method that is clinically used for pancreatic cancer screening is EUS, commonly performed in combination with cross-sectional imaging modalities such as MRI. The diagnostic yield of EUS ranges from 10% to 50%. Brentnall and colleagues prospectively studied 14 patients who had 2 or more family members in more than 2 generations with a history of pancreatic cancer. Patients were assessed with EUS, ERCP, CEA, and CA 19-9. Seven of 14 patients had abnormal findings on EUS and ERCP. These 7 patients underwent pancreatic resections, which showed evidence of intraductal dysplasia in all specimens [11]. Rulyak [12] and colleagues studied 35 patients from 13 familial pancreatic cancer. EUS was the initial test followed by ERCP in cases of symptomatic individuals. Twelve of 35 patients had abnormalities on both EUS and ERCP and underwent pancreatectomy, with histology showing pancreatic dysplasia on all 12 cases. Follow-up of the 35 patients varied from 1 to 48 months, and none had pancreatic cancer at follow-up [12].

Future Prospects

There is a need for the development of novel methods for early detection of pancreatic cancer at the earliest stages and particularly for premalignant lesions.

New Biomarkers

Plectin-1

Plectin-1 is a high molecular weight–protein normally expressed in several tissues, including skin, muscle, and brain, required in the maintenance of mechanical integrity and viscoelasticity properties of tissues. Studies have demonstrated that plectin-1, which is normally expressed in the cytoplasm, is overexpressed in the cell membrane of PDAC cells compared to normal pancreatic ductal cells [13].

Glypican-1

Glypican-1 is a cell membrane proteoglycan, implicated in the control of cellular growth and differentiation and is also expressed in breast and pancreatic cancer–derived exosomes. Melo and colleagues analyzed 56 patients with pancreatic cancer, 6 with pancreatitis, and 20 healthy donors and demonstrated that exosomes from pancreatic cancer patients express higher levels of glypican-1 than healthy subjects. Glypican-1 circulating exosomes correlate with tumor burden and could be used to assess prognosis and pancreatic cancer recurrence [14].

Three-Biomarker Panel in Urine

Urinary metabolomics studies offer an opportunity to identify tumor-associated perturbations of cellular metabolism reflecting changes that occur in the tumor micro- and macroenvironment. Such is the case with 3 proteins recently reported to be useful as pancreatic cancer biomarkers: REG1A, TFF1, and LYVE1 [15]. The 3 markers have been found to be increased in urine samples from patients with pancreatic cancer compared with healthy controls.

New Imaging Methods

Single-Source, Dual-Energy, Spectral Multidetector Computed Tomography

Pancreatic cancers are commonly hypoattenuating while Kim and colleagues have found that 27% of pancreatic adenocarcinomas smaller than 2 cm were isoattenuating by (MDCT), which results in lesions potentially being missed. In comparison with a weighted-average 120-kVp data set, generation of pure 80-kVp data at dual-source dual-energy MDCT improves differentiation of attenuation values between malignant tumors of the pancreas and normal pancreas.

The single-source, dual-energy system utilizes a single radiograph beam source that switches energy between 80 and 140 kVp, offers the ability to detect hypovascular pancreatic cancers at lower viewing energy levels, diminishing the number of isoattenuating early-stage tumors [16]. This technique can also be performed with a dual-source system with two independent x-ray tubes [17].

Hybrid Positron Emission Tomography–Magnetic Resonance Imaging

Fusion imaging studies have demonstrated an improved quality of differentiation of pancreatic cancer from benign lesions. MRI provides useful structural and functional tumor information. Positron emission tomography (PET), is an effective predictor of staging and prognosis in cancer patients [18]. A study has demonstrated that hybrid PET-MRI is significantly more accurate (96.6%) than PET-CT (86.6%) in terms of performing a diagnosis of pancreatic cancer. PET-MRI fusion also offers information such as involvement of the main pancreatic duct or collateral veins, peripancreatic anatomic borders, and superior mesenteric artery or celiac artery, which are important predictive factors for respectability. PET/MR imaging, which provides anatomic information, as well as PET and DW imaging, can be useful in the detection and characterization of lymph nodes [19] which is an important factor in the accurate prediction of a patient's prognosis [30].

Novel Endoscopic Ultrasound Techniques

Endoscopic methods may help provide better screening yield for pancreatic cancer, because of the information about precursor lesions or prediction of which precursor lesions

are likely to behave in an aggressive manner. Some of these techniques are briefly described below.

Contrast-Enhanced Harmonic Endoscopic Ultrasound

This relatively new technique, based on the detection of signals from microbubbles in vessels, can visualize both parenchymal perfusion and microvasculature in the pancreas for the neoplastic solid components as hyper enhanced lesions [20].

Endoscopic Ultrasound Elastography

Elastography is a relatively new technique applied to EUS imaging to distinguish different tissues based on their elastic properties. Cancerous tissue is known to be stiffer than corresponding healthy tissue [21].

Endoscopic Ultrasound–Guided Fine-Needle Aspiration and Pancreatic Juice Sampling

Combining EUS guided fine-needle aspiration cytopathology analysis with KRAS mutation assay and Detection of TP53 mutations in secretin-stimulated pancreatic juice increased the sensitivity and accuracy of cytopathology [22].

Needle-Based Confocal Laser Endomicroscopy

Needle-based confocal laser endomicroscopy (nCLE) is a newly developed endomicroscopic technique that enables imaging of the mucosal layer at a subcellular level of resolution. In pancreatic cancer, nCLE can detect vascular leakage with irregular vessels and leakage of fluorescein into the tumor [23].

Duodenal Spectroscopy

The periampullary duodenal mucosa has genetic and environmental sharing with of the pancreas [24]. Based on this Mutual and colleagues conducted a case-control study to evaluate low-coherence-enhanced backscattering spectroscopy to predict the probability of pancreatic cancer by analyzing the duodenal mucosa.

Conclusion

While the early diagnosis of pancreatic cancer remains challenging, improvements in diagnostic technology and methodologies will hopefully translate into improved outcomes. Screening of high-risk individuals using EUS and/or MRI is recommended and shows promise in early detection. Several potential novel biomarkers and imaging techniques are under evaluation for detecting premalignant and early malignant changes in the pancreas. Further advancement and progress in these techniques will help in identifying precursor lesions while they are still resectable.

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