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TOPIC HIGHLIGHT

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Strategies for early detection of resectable pancreatic cancer

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Abstract

Pancreatic cancer is difficult to diagnose at an early stage and generally has a poor prognosis. Surgical resection is the only potentially curative treatment for pancreatic carcinoma. To improve the prognosis of this disease, it is essential to detect tumors at early stages, when they are resectable. The optimal approach to screening for early pancreatic neoplasia has not been established. The International Cancer of the Pancreas Screening Consortium has recently finalized several recommendations regarding the management of patients who are at an increased risk of familial pancreatic cancer. In addition, there have been notable advances in research on serum markers, tissue markers, gene signatures, and genomic targets of pancreatic cancer. To date, however, no biomarkers have been established in the clinical setting. Advancements in imaging modalities touch all aspects of the clinical management of pancreatic diseases, including the early detection of pancreatic masses, their characterization, and evaluations of tumor resectability. This article reviews strategies for screening high-risk groups, biomarkers, and current advances in imaging modalities for the early detection of resectable pancreatic cancer.

Key words: Early detection; Resectable; Pancreatic cancer; Screening; High-risk group; Biomarker; Imaging

Core tip: To improve the prognosis of patients with pancreatic cancer, it is essential to detect tumors at early stages, when they are resectable. The cancer of the pancreas screening program has reached several conclusions and recommendations for the management of patients who are at an increased risk of familial pancreatic cancer. Furthermore, genetic, epigenetic, and proteomics research have improved the understanding of the mechanisms of this disease, potentially offering biomarkers that could allow the cancer to be detected early. This article reviews strategies for the early detection of resectable pancreatic cancer.

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INTRODUCTION

Pancreatic cancer is an especially lethal malignancy, with a mortality rate that almost equals its incidence. After pancreatic cancer is diagnosed, the 1-year relative survival rate is only 24%, and the 5-year overall survival rate is only 5%[1,2]. However, rates of overall survival have been improving over the past decades, for both resected and non-resected cases[1]. These improvements are believed to have resulted from more optimal patient selection, refinements in surgical techniques, and better postoperative patient care, in addition to the development of effective adjuvant therapies. In cases of pancreatic carcinoma,

complete surgical resection with adjuvant chemotherapy offers the best outcomes[3]. However, over 80% of patients with pancreatic cancer present with an unresectable primary tumor and distant metastasis at the time of diagnosis[4]. Of patients with resectable pancreatic cancers, only 15% have earliest-stage cancers (T1 or T2 tumors without lymph node metastases), which are associated with better survival[5,6]. Thus, only 2%-3% of all patients diagnosed with pancreatic cancer present with earliest-stage cancer. Among the patients with pancreatic cancer who undergo surgical resection, the 5-year survival rate is 15%-40%[7]. In a study of operated pancreatic cancers from the Japanese Pancreatic Cancer Registry, it was observed that patients with stage I tumors < 2 cm in size had considerably better survival (58% alive at 5 years) than patients with stage Ⅱb tumors (17% alive at 5 years)[1]. In another study, 100% 5-year survival was observed among 79 patients who had tumors < 1 cm and had undergone curative resection[8].

Recently, a valuable analysis about the timing of the genetic evolution of pancreatic cancer was reported[9]. The authors indicated at least a decade between the occurrence of the initiating mutation and the birth of the parental, non-metastatic founder cell. Furthermore, at least five more years are required for the acquisition of metastatic ability and patients die an average of two years thereafter. These data provide novel insights into the genetic features underlying pancreatic cancer progression and define a broad time window of opportunity for early detection to prevent deaths from metastatic disease. For these reasons, significant efforts have been invested towards identifying high-risk groups, sensitive biomarkers, and accurate imaging modalities for pancreatic cancer. Each of these advancements can facilitate the early diagnosis of pancreatic cancer that is resectable or potentially resectable.

CURRENT CRITERIA FOR RESECTABILITY

In the absence of metastatic disease, pancreatic cancer cases are classified into three main categories: resectable, borderline resectable, and unresectable. Recent revisions of the National Comprehensive Cancer Network (NCCN) guidelines have attempted to distinguish tumors that are clearly resectable from those that are borderline resectable[10]. Further, the NCCN guidelines provide a definition for radiographically resectable tumors. The specific NCCN guidelines have been quoted below[10].

Tumors considered "resectable" should demonstrate the following (1) No distant metastases; (2) No radiographic evidence of superior mesenteric vein (SMV) or portal vein (PV) distortion; and (3) Clear fat planes around the celiac axis, hepatic artery, and SMA.

Tumors considered "borderline resectable" include the following: (1) No distant metastases; (2) Venous involvement of the SMV or PV with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing safe resection and replacement; (3) Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis; and (4) Tumor abutment of the SMA not to exceed > 180° of the circumference of the vessel wall.

To improve the prognosis of patients with pancreatic cancer, it is essential to detect tumors at early stages, when they are more likely to be resectable.

SCREENING HIGH-RISK GROUPS TO FACILITATE EARLY DIAGNOSIS OF PANCREATIC CANCER

As presented in Table 1, previous studies have identified a variety of risk groups and factors for developing pancreatic cancer. An elevated risk of developing pancreatic cancer is associated with being a current smoker[11], African-American[4], over 55 years old[4], male[4], obese[12], previously diagnosed with intraductal papillary mucinous neoplasms (IPMNs)[13], or previously diagnosed with diabetes[12,14]. Additionally, family history can be used to identify some individuals who have a high risk of developing pancreatic cancer. An increased risk of pancreatic cancer has been linked to family histories of pancreatic cancer[15,16], chronic pancreatitis[17,18], hereditary pancreatitis[19,20], Peutz-Jeghers syndrome[21,22], familial atypical multiple mole melanoma, cystic fibrosis[23], and familial cancer syndromes, which include Lynch syndromes[24,25], familial adenomatous polyposis pAPC mutation, and hereditary breast and ovarian cancer syndrome with *BRCA1* and *BRCA2* mutations[26,27]. This section of our review focuses on screening guidelines, the importance of new-onset diabetes, and the identification of precancerous lesions for the early detection of resectable pancreatic cancer.

Screening programs

The cancer of the pancreas screening (CAPS) program is one of largest pancreatic screening initiatives to date. Results from the CAPS 1 and CAPS 2 studies show that early pancreatic neoplasia can be detected by screening asymptomatic patients[28,29]. In the CAPS 1 study, the diagnostic yield of screening was 5.3%. Most encouragingly, the patient who was diagnosed with pancreatic cancer as a consequence of screening is still alive and disease free more than 5 years after surgery[28]. CAPS 2 screening was performed using annual endoscopic ultrasound (EUS) and computed tomography (CT). Once an abnormality had been detected, endoscopic retrograde cholangiopancreatography (ERCP) was offered. Of the 72 high-risk patients, eight had pancreatic neoplasia confirmed by surgery or fine-needle aspiration biopsy (FNA), constituting a 10% yield of screening. The CAPS 3 study is an ongoing multicenter prospective controlled cohort study that involves annual screening using EUS and magnetic resonance cholangiopancreatography (MRCP).

Table 1 Risk factors for pancreatic cancer

Variables	Association	Ref.
Non-genetic risk factors		
Age	Ages 55-64 yr: 20.7% of cases; ages 65-74 yr: 25.8% of cases; ages 75-84 yr: 27.8% of cases; age 85 + yr: 13.3% of cases	[4]
Gender	The incidence rate is 13.8 per 100000 men and 10.8 per 100000 women	[4]
Smoking	Most established risk factor for PC. Risk increases significantly with greater intensity: ≥ 30 cigarettes/day (OR = 1.75, 95%CI: 1.27-22.42); duration ≥ 50 yr (OR = 2.13, 95%CI: 1.25-3.62); and cumulative smoking dose ≥ 40 pack-years (OR = 1.78, 95%CI: 1.35-2.34)	[11]
Obesity	Obese individuals (BMI ≥ 30) have a slightly higher risk (RR: 1.19) of developing PC compared with normal-weight individuals (BMI < 25)	[12]
Race	15.5 males and 12.6 females per 100000 in African-Americans, while 8.4 males and 6.9 females per 100000 for Asians/Pacific Islanders	[4]
Diabetes mellitus (DM)	Meta-analysis from 35 cohort studies revealed a RR ratio of 1.94 (95%CI: 1.66-62.27) between type 2 DM and PC. 40%-100% increases in the risk of PC are observed with established diabetes	[12,14]
New-onset diabetes	New-onset diabetes is associated with a four- to seven-fold increase in risk, such that 1%-2% of patients with recent-onset diabetes will develop PC within 3 yr	[30]
Intraductal papillary mucinous neoplasms	Standardized incidence ratio 16	[13]
Hereditary cancer syndromes		
Familal pancreatic cancer	1 first-degree relative: 4.6-fold increased risk (95%CI: 0.5-16.4); ≥ 2 first-degree relatives: 6.4-fold increased risk (95%CI: 1.8-16.4); ≥ first-degree relatives: 32-fold increased risk (95%CI: 10.2-74.7)	[15,16]
Chronic pancreatitis	An incidence ratio of 14-18 observed for the development of PC in CP cases, which is further increased by cigarette smoking	[17,18]
Hereditary pancreatitis	A 53-fold (95%CI: 23-105) increased risk for developing PC and a lifetime risk (age 70 yr) of PC of 30%-40% in comparison with normal. RR increases further in smokers	[19,20]
Peuts-Jeghers	132-fold (95%CI: 44-261) increased risk of PC compared with the general population	[21,22]
Lynch syndrome	8.6-fold (95%CI: 4.7-15.7) increased risk for developing PC compared with the general population. An estimated 3.68% (95%CI: 1.45%-45.88%) lifetime (age 70 yr) risk of PC	[24,25]
Hereditary breast and ovarian cancer	BRCA2 germline mutation carriers have a 5% lifetime risk of PC in comparison with 1.78% for controls. BRCA1 mutation is 2.26-times that of the normal population	[26,27]

PC: Pancreatic cancer.

CAPS 3 is also investigating magnetic resonance imaging (MRI) with secretin and a panel of candidate DNA and protein markers (in serum and pancreatic juice) as indicators of pancreatic neoplasms. Carbohydrate antigen 19-9 (CA19-9), macrophage inhibitory cytokine-1 (MIC-1), DNA hypermethylation, and *K-ras* gene mutations are presently under investigation as potential markers. The CAPS consortium has reached several conclusions and recommendations for the management of patients who are at an increased risk of familial pancreatic cancer[16]. The CAPS consortium specifically agreed that the following individuals were candidates for screening: first-degree relatives (FDRs) of patients with pancreatic cancer in a familial pancreatic cancer kindred with at least two affected FDRs; patients with Peutz-Jeghers syndrome; and carriers of *p16, BRCA2*, and hereditary non-polyposis colorectal cancer (HNPCC) mutations with at least one affected FDR. The consortium agreed that initial screening should include EUS, potentially with MRI or MRCP, but excluding CT and ERCP. The consortium did not agree on optimal screening modalities, intervals for follow-up imaging, or the use of EUS-FNA to evaluate cysts.

In general, screening was recommended for high-risk individuals. However, additional evidence is needed regarding the sensitivity and cost-effectiveness of screening, as well as the choice of management strategy for patients with lesions that are detected by screening.

New-onset diabetes

The CAPS approach does not contribute to the early detection of pancreatic cancers that have completely sporadic onsets. To identify early pancreatic cancers in sporadic groups, it may be possible to screen patients at the onset of diabetes mellitus. The new onset of diabetes mellitus is occasionally associated with pancreatic carcinoma that is otherwise clinically silent and, indeed, is potentially resectable[30]. A population-based cohort study of 2122 diabetic individuals identified 18 (0.8%) patients who developed diabetes at age 50 years or older and were diagnosed with pancreatic cancer in the next 3 years. In this cohort of individuals who were newly diagnosed with diabetes, the ratio of observed-to-expected pancreatic cancer incidence was 7.9 (95%CI: 4.7-12.5)[31].

Diabetes is highly prevalent in cases of pancreatic cancer, even for early-stage pancreatic cancers[32-36]. Specifically, 50% of patients with stage I or II pancreatic cancer had diabetes[37]. Tsuchiya *et al*[36] observed abnormal glucose tolerance in 61% of patients with small pancreatic cancers (≤ 2 cm). A study of especially small pancreatic cancers (< 10 mm) noted a 33% prevalence of diabetes[38]. Because diabetes arises in almost half of patients with pancreatic cancer, it is an attractive target for early pancreatic cancer screening.

Identification of precancerous lesions

Precancerous lesions are ideal targets for early identification because they can be treated before developing into invasive cancer. The majority of pancreatic masses treated by surgical resection are IPMNs, which have been increasingly recognized as precursors to pancreatic ductal adenocarcinoma[39]. Post-resection cure rates are very high for IPMN that does not have an associated infiltrating ductal pancreatic adenocarcinoma[40,41]. Pancreatic intraepithelial neoplasias (PanINs) are small neoplasms ($\leqslant$ 5 mm) that are mostly found in the head of the gland and are thought to be the most common precursor to invasive pancreatic ductal adenocarcinoma[39]. Most precancerous lesions (and especially PanINs) can only be identified reliably after surgical resection. Because many healthy individuals have low-grade PanINs that will never progress to clinically important neoplasms[42], markers are needed to help differentiate between neoplastic and non-neoplastic pancreatic lesions, as well as to indicate the presence of microscopic high-grade PanINs that might be suggestive of future pancreatic cancer risk.

The most challenging aspect of screening and surveillance programs is the management of asymptomatic pancreatic lesions that are detected by imaging tests. It is essential to have individualized decision-making within multidisciplinary programs and prospective research studies.

BIOMARKERS THAT FACILITATE EARLY DIAGNOSIS OF PANCREATIC CANCER

Biomarker screening is one possible approach for identifying these early lesions. To date, over 2000 studies of possible biomarkers have been published[43]. Yet, biomarkers for the detection of small pancreatic cancer have not been validated.

Serum markers

CA19-9 is a sialylated Lewis (a) antigen; it is a carbohydrate that is produced by exocrine epithelial cells and is normally absorbed onto erythrocyte surfaces. The measurement of CA19-9 levels has never been shown to be effective as a screening test for pancreatic cancer. In a study of 10162 asymptomatic individuals, abnormal CA19-9 levels were identified in only 18 (0.2%) persons[44]. Although this study used a variety of screening tests, only four pancreatic cancers (0.04%) were detected. Pleskow *et al*[45] performed one of the first studies that established CA19-9 as a promising biomarker in pancreatic cancer. In this study of 261 patients (including 54 with pancreatic cancer), the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CA19-9 were 70%, 87%, 59%, 92% and 84%, respectively. In addition, preoperative CA19-9 test levels constitute false positives in the setting of biliary obstruction, which is present in the majority of patients with pancreatic cancer and various benign conditions related to the pancreas and biliary tract[46]. There is some evidence that preoperative CA19-9 measurements can help determine whether a pancreatic cancer is resectable[47]. Maithel *et al*[48] reported a strong association between preoperative CA19-9 values and the identification of unresectable pancreatic cancer that could not be recognized on diagnostic imaging studies. They recommend staging laparoscopy for pancreatic cancers associated with CA19-9 levels that exceed 130 U/mL.

Carbohydrate antigens of mucin-1 (MUC-1) have been investigated as potential means of improving on the performance of CA19-9[49]. Yet, none of the assays used to detect MUC-1 carbohydrate epitopes have proven to be superior to CA19-9 measurements. PAM-4 can be used to detect MUC-1 proteins expressed in pancreatic cancer with a greater specificity than MUC-1 proteins expressed in other cancers[50]. Additionally, initial studies have shown that an enzyme-linked immunosorbent assay directed at detecting circulating MUC-1 epitopes is more sensitive and specific than CA19-9 for identifying patients with pancreatic cancer[50].

In a recent study, serum MIC-1 was determined to be more sensitive than CA19-9 as a marker of pancreatic cancer[51]. MIC-1 belongs to the transforming growth factor-β superfamily, which was first identified in the context of macrophage activation[52]. MIC-1 is overexpressed in pancreatic, colon, prostrate, breast, gastric, and several other types of cancers[53-55], and therefore, it may prove useful for diagnosing other cancers[56]. In an investigation of pancreatic cancer and MIC-1 levels, 90% of patients with resectable pancreatic cancer had MIC-1 levels that were more than 2 standard deviations greater than those in age-matched controls. By comparison, only 62% of patients with resectable pancreatic cancer had elevated CA19-9. Elevated MIC-1 was observed to be independent of TNM stage. Further, elevated MIC-1 was observed in six of seven patients who had T1 or T2 cancers, but elevated CA19-9 was observed in only two of these seven patients[57]. Based on these findings, serum MIC-1 may prove to be useful as a component of pancreatic screening protocols for detecting early stage pancreatic cancers in high-risk groups[28,58].

Proteomics

Proteomics approaches have also been employed in an attempt to identify protein markers of pancreatic cancer[59-62]. Several groups have identified protein fragments in serum using surface-enhanced laser desorption ionization, which appears to have found protein fragments that function as diagnostic makers at least as effectively as does serum CA19-9[63,64]. Pancreatic cancer proteins have also been identified in serum using matrix-associated laser desorption ionization, which is another mass spectrometry approach[65]. Proteomics studies have identified several important proteins that are associated with pancreatic tumorigenesis, including galectin-1, gelsolin, lumican, 14-3-3 protein sigma, cathepsin D, cofilin, moesin, and plectin-1[60,66,67]. Gelsolin and lumican were later tested in plasma, showing an 80% sensitivity and a 95% specificity

as a composite biomarker for separating early stage pancreatic cancer patients (stages Ⅰ and Ⅱ) from healthy controls and patients with chronic pancreatitis (*via* selected reaction-monitoring-based targeted proteomics assays)[68]. The application of proteomics to the study of pancreatic cancer is still in its early stages and remains challenging. Yet, despite being an emerging technology, proteomics has already provided fundamental information that has improved our understanding of this disease's mechanisms. Further, proteomics potentially offers solutions for the early detection of this cancer.

Genetic and epigenetic markers

K-ras mutations are present in up to 90% of pancreatic ductal adenocarcinomas[69,70]. Accordingly, *K-ras* mutants have been thoroughly investigated as markers of pancreatic adenocarcinoma. In addition to invasive pancreatic cancers, K-ras mutations also occur in patients with chronic pancreatitis, persons who smoke, and PanINs in patients who do not have pancreatic cancer[69]. Additionally, mutant K-ras is detected in the blood of patients with advanced-stage pancreatic cancers more commonly than it is detected in the blood of patients with less advanced pancreatic cancers[71,72].

TP53 mutations have been extensively investigated as possible diagnostic markers of a variety of cancers. In the case of invasive pancreatic cancer, however, such mutations do not normally occur until late in the neoplastic process. *TP53* gene mutations are found in 70% of invasive pancreatic ductal adenocarcinomas[73]. Mutations occur throughout the *TP53* gene, although several nucleotide hot spots have been identified, at which mutations are especially common[74].

The strategy of combining markers can optimize the diagnosis of pancreatic cancer through molecular examination[75]. In a study of a combined marker panel, the combination of methylated p16, mutant K-ras, and a functional yeast assay for *TP53* mutations was investigated[75]. The authors concluded that the presence of *TP53* mutations was the most specific. With improvements in the technology for detecting mutations, *TP53* mutations in pancreatic juice may underpin an effective diagnostic strategy.

Pancreatic cancer is both a genetic and an epigenetic disease[76,77]. Various genes are methylated as pancreatic cancer arises, and non-neoplastic pancreatic tissues rarely show methylation of these same genes. Genes that are methylated in the process of pancreatic cancer formation are p16[78], RELN[79], DAB1[79], ppENK[80], Cyclin D2[81], SOCS1[82], *SPARC*[83], TSLC1[84], and others[85,86]. Because the methylation of some of these genes can be detected through methylation-specific polymerase chain reaction, and because some of these genes are also highly expressed in pancreatic cancers, epigenetic markers may provide an opportunity for the early detection of pancreatic cancers.

Other potential markers

Promising biomarkers have also been established for predicting the effectiveness of chemotherapy and immune-based therapy. The human equilibrative nucleoside transporter (hENT1) protein transports gemcitabine into cells. In a prospective randomized trial (RTOG9704), hENT1 protein expression was associated with increased overall survival and disease-free survival in pancreatic cancer patients who received gemcitabine, but not in those who received fluorouracil. These findings are supported by preclinical data; the gemcitabine transporter hENT1 is therefore a molecular and mechanistically relevant predictive marker of benefit from gemcitabine in patients with resected pancreatic cancer[87]. In addition to hENT1, key determinants of gemcitabine cytotoxicity include the activities of deoxycytidine kinase (dCK). Indeed, high levels of hENT1 and dCK predict longer survival times in patients with pancreatic cancer who are treated with adjuvant gemcitabine[88].

Mesothelin is a glycoprotein expressed on normal mesothelial cells. It is overexpressed in several histologic types of tumors, including pancreatic adenocarcinomas. A soluble form of mesothelin has been detected in patients with ovarian cancer and malignant mesothelioma, and has been found to have prognostic value. Circulating mesothelin is also a useful biomarker for pancreatic cancer. Furthermore, mesothelin-specific T cells can be induced in patients with pancreatic cancer. This suggests that mesothelin is a potential target for immune-based intervention strategies in pancreatic cancer[89]. Although it is not yet clear how these markers specifically relate to the early diagnosis of pancreatic cancer, they may be clinically useful for treatment selection.

Investigations of pancreatic juice have involved both genetic and epigenetic markers for pancreatic cancer. To date, mutant K-ras, p53 mutations, DNA methylation alterations, mitochondrial DNA mutations, and other potential genetic and epigenetic markers have been investigated in pancreatic juice[75]. The MitoChip allows investigations of the mitochondrial genome. Early studies using this novel technology suggest that it can be used to detect mitochondrial mutations in pancreatic juice samples that are taken from patients with pancreatic cancer[90].

Genetic, epigenetic, and proteomics research have improved the understanding of the mechanisms of pancreatic cancer, potentially offering biomarkers that could allow its early detection. It is critically important to validate the utility of these biomarkers in clinical setting as soon as possible.

IMAGING FOR THE EARLY DIAGNOSIS OF PANCREATIC CANCER

Every aspect of the clinical management of pancreatic diseases is influenced by imaging studies. Specific examples include the early detection and characterization of pancreatic masses, the identification of anatomical variants, investigations of local and vascular involvement, the determination of perineural and lymphatic invasion, margin assessments, the detection of distant metastases,

and assessments of tumor resectabilty[91]. Because effective screening markers remain elusive, imaging remains the primary form of screening for cases of familial pancreatic cancer, in addition to its more routine use in the staging and management of pancreatic cancer[28,29,92-94]. Recently, imaging accuracy has been improving as a result of technological improvements. However, imaging still fails to detect many lesions that are under a centimeter in size.

EUS

In comparison with other approaches to imaging, EUS has been growing in popularity. Indeed, EUS offers a large variety of benefits. First, it can detect pancreatic lesions and intraductal papillary mucinous neoplasms that are less than a centimeter in size with a greater sensitivity than is offered by abdominal ultrasonography, CT, or MRI. Second, EUS accurately judges deep tumors. Third, EUS-guided FNA enables lesion biopsies and has an excellent diagnostic accuracy (92%)[95]. Fourth, EUS detects lymph node metastasis and vascular infiltration with greater sensitivities than are offered by CT imaging. More specifically, advancements in contrast-enhanced EUS technology could improve the characterization of vessels in the desired lesions, the accuracy of tumor staging, the accuracy of tumor follow-up, and differential diagnosis. Additionally, improvements in EUS elastography could advance real-time evaluations of tissue stiffness. Finally, hybrid imaging (such as CT/ultrasonography or CT/ultrasonography/MRI) may offer an opportunity to improve the detection and characterization of focal lesions[96].

For lesions < 2 cm, EUS is associated with a sensitivity and accuracy that approach 100%, as well as a specificity > 95%[97-100]. In an analysis of EUS-FNA for pancreatic lesions < 3 cm, Tadic *et al*[101] demonstrated a sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of 68%, 100%, 100%, 73%, and 83%, respectively. Based on these results, it appears that EUS has become quite capable of providing histological evidence, for which there is a great needed. Therefore, EUS should be performed wherever sufficient expertise is available.

Multi-detector CT

The resolution and diagnostic capabilities of CT scanners have improved to remarkable extents. Currently, 64-section thin-cut intravenous contrast-enhanced multi-detector CT (MDCT) is the tool of choice for radiological investigations. Scanning occurs in a sequence of phases: non-contrast, arterial, pancreatic parenchymal, and portal venous. Key features of MDCT are its rapid anatomic coverage and excellent spatial resolution[102]. When employed for the detection of pancreatic cancers, the sensitivity of CT ranges from 75% to 100%, and its specificity ranges from 70% to 100%[97,99,102-105]. Yet, for lesions ≤ 2 cm in size, this sensitivity diminishes to 68%-77%[97,103], with an accuracy of 77%[99].

The diagnosis of small pancreatic carcinoma is aided by findings of dilatation of the main pancreatic duct (MPD) and associated pancreatitis[106]. In the case of associated pancreatitis, a contrasting effect is evident between the areas of the pancreatic parenchyma proximal and distal to the site of the MPD obstruction[107,108].

MRI/MRCP

CT and MRI/MRCP are the primary investigations that are most commonly performed for the diagnosis and staging of pancreatic cancers. The choice between CT and MRI/MRCP is generally determined by the availability these individual modalities at medical centers, as well as the availability of the technical expertise that is necessary for interpreting and reporting their results. Fusari *et al*[109] found that, for the diagnosis of pancreatic cancer, MRCP offered a sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of 100%, 88%, 98%, 97%, and 100%, respectively. They also found that MRCP, when evaluating the resectability of pancreatic carcinomas, offered a sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of 88%, 100%, 90%, 100%, and 70%, respectively. As outlined by Miller *et al*[100], the addition of MRCP to CT can offer substantial benefits to tumor diagnosis and staging in several contexts. MRI's excellent contrast resolution is beneficial for detecting small tumors on gadolinium-enhanced fat-suppressed images.

PET

PET is a functional imaging modality that can detect metabolic alterations in tumors, which may precede notable morphological alterations. The radioactive tracer ^{18}F-fluorodeoxyglucose (FDG) has been used extensively in the PET imaging of malignant tumors. PET/CT can accurately detect small primary pancreatic lesions, distant metastases, and post-surgery recurrences. As a result of these capabilities, PET/CT has become increasingly important in the diagnosis and management of pancreatic cancer[110-112]. Elevated glucose metabolism has been found in the precursor lesions of pancreatic cancer, which suggests that there may be an opportunity to detect these changes using PET/CT, and thereby improve the timeliness of diagnosis and patient outcomes[113].

We have previously investigated the role of FDG-PET with dual-time point evaluation in cases of small pancreatic cancer[114]. When investigated using FDG-PET with dual-time point evaluation, all TS1 tumors (< 20 mm) had higher standardized uptake values in the delayed phase than in the early phase, which suggested that the lesions were malignant tumors. These results indicate that FDG-PET with dual-time point evaluation is a useful modality for diagnosing small pancreatic cancers.

A recent meta-analysis[115] regarding the detection of pancreatic carcinoma found a pooled sensitivity of 90.1% for PET-CT, which was substantially better than the 81.2% pooled sensitivity of EUS. However, PET-CT was also associated with a pooled specificity of 80.1%,

while EUS had a pooled specificity of 92.3%. These results are similar to the findings of two previously published reviews of the literature on the same topic[116,117]. The role of FDG-PET in the early detection and accurate staging of pancreatic cancer is controversial. We suggest that future research should definitely focus on the development of more specific PET tracers for pancreatic ductal adenocarcinoma.

CONCLUSION

Despite advancements in surgical techniques and adjuvant treatment, the prognosis of pancreatic cancer has only improved marginally over the past years. Future research should continue and expand recent investigations of screening for high-risk groups, sensitive biomarkers, and imaging modalities for the early diagnosis of resectable pancreatic cancer. Recent studies have successfully identified pre-invasive neoplasms using accurate pancreatic imaging tests. These advancements are encouraging. They attest to the importance of additional studies that are aimed at identifying individuals at a substantially increased risk of developing pancreatic neoplasia.

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