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REVIEW

Challenges in diagnosis of pancreatic cancer

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Abstract

Pancreatic cancer is a growing source of cancer related death, yet has poor survival rates which have not improved in the last few decades. Its high mortality rate is attributed to pancreatic cancer biology, difficulty in early diagnosis and the lack of standardised international guidelines in assessing suspicious pancreatic masses. This review aims to provide an update in the current state of play in pancreatic cancer diagnosis and to evaluate the benefits and limitations of available diagnostic technology. The main modalities discussed are imaging with computed tomography, magnetic resonance imaging, endoscopic ultrasound and positron emission tomography and tissue acquisition with fine needle aspiration. We also review the improvements in the techniques used for tissue acquisition and the opportunity for personalised cancer medicine. Screening of high risk individuals, promising biomarkers and common mimickers of pancreatic cancer are also explored, as well as suggestions for future research directions to allow for earlier detection of pancreatic cancer. Timely and accurate diagnosis of pancreatic cancer can lead to improvements in the current poor outcome of this disease.

Key words: Pancreatic cancer; Diagnosis; Challenges; Imaging; Biomarkers; Screening; Endoscopic ultrasound; Pitfalls

Core tip: Pancreatic cancer is becoming a leading cause of cancer related death in Western societies. Rapid and accurate diagnosis of a pancreatic mass is crucial for improving outcomes. Current practice utilises multi-detector computed tomography and/or magnetic resonance imaging, with a dedicated pancreas protocol as the initial modality. Endoscopic ultrasound is the preferred method to further evaluate pancreatic masses as it has more superior diagnostic accuracy and can provide tissue acquisition. Pitfalls in diagnosis of pancreatic

cancer are discussed, as careful recognition of these conditions is important. There are exciting developments of new diagnostic techniques that open the possibility of personalised cancer medicine.

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INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer related death in Western societies and is projected to be the second leading cause within a decade. It has an average annual incidence rate of 12.5 per 100000 population (which is 3% of all cancers) in America, but has a disproportionately high mortality, with an average annual death rate of 10.9 per 100000[1]. Pancreatic cancer is difficult to be diagnosed at an early stage, with the vast majority of cancers found to be already metastatic at the time of initial diagnosis. Only 9.7% of pancreatic cancer are at a local stage at time of diagnosis[2]. These poor survival rates have not changed significantly in nearly 40 years.

Ductal adenocarcinoma and its variants account for over 90% of pancreatic malignancies. Presenting features of this disease may include weight loss, jaundice, malabsorption, pain, dyspepsia and nausea; however, many patients are asymptomatic and no early warning signs of pancreatic cancer have been established.

Known risk factors for pancreatic cancer include cigarette smoking (relative risk increase of 2.5 times[3]), high body mass index and lack of physical activity[4], diabetes[5] and chronic pancreatitis[6]. Furthermore, there are also a number of inherited cancer syndromes linked to pancreatic cancer including Hereditary Breast and Ovarian Cancer Carriers of the BRCA1 or BRCA2 germline mutations, familial atypical multiple mole melanoma syndrome (FAMMM), Peutz-Jeghers syndrome, hereditary pancreatitis, Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome) and familial pancreatic cancer. These higher risk groups may be a good target for screening and early diagnosis programs.

Surgical resection is the only curative treatment for pancreatic cancer. Unfortunately, because of late presentation, only 15% to 20% of patients are candidates for pancreatectomy. Furthermore, prognosis is poor, even after a complete resection. Five year survival after pancreaticoduodenectomy, or Whipples procedure, is approximately 21% for negative margin resections (R0) and 11% for microscopically positive margin resections (R1)[7]. Even in patients with negative margin resections with presumed curative intent, up to 71% can have disease recurrence[7].

The motivation for this research is the dismal outcomes for pancreatic cancer that have failed to significantly improve; it is this that is the key problem to be solved. The main focus of this review is to describe the current state of play in pancreatic cancer diagnosis. Rapid and accurate diagnosis of a pancreatic mass is crucial for improving outcomes. After evaluating the evidence underpinning all of the widely used modalities for diagnosis, we intend to make a comparison of these modalities and provide an evidence-based algorithm for diagnosis.

The main objective of this review was to evaluate and compare the suitability and accuracy of the current diagnostic modalities that exist for pancreatic cancer. We are currently lacking effective diagnostic and screening modalities to diagnose pancreatic cancer at an early, and therefore more likely curative stage. Therefore, it is valuable to have a thorough understanding of the currently available diagnostic technology, including its benefits and limitations, in order to provide direction for future research. Pitfalls and mimickers of pancreatic cancers, biomarkers and the current screening programs in high risks individuals will also be discussed.

LITERATURE SEARCH

A MEDLINE search was conducted using the following keywords and phrases: "pancreatic cancer, diagnosis, imaging, biomarkers, screening, endoscopic ultrasound, pitfalls", with a focus on more recently published research. In addition, we performed a manual review of the reference lists of the primary and review articles to ensure identification of all relevant articles. In particular, large scaled meta-analyses and systematic reviews were preferred.

RESULTS

Diagnosis relies on imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and endoscopic ultrasound (EUS) that are used along with tissue acquisition. Early detection is the only way of identifying small cancers and proceeding with curative surgery. We describe the different diagnostic modalities that currently exist, evidence underpinning their use and compare the benefits and disadvantages of each. Table 1 below provides a summary of our findings and Figure 1 shows a suggested algorithm based on our findings for the evaluation of a patient with pancreatic cancer.

CT SCANNING

Multi-detector computed tomography (MDCT) is the most widely available and best-validated tool for imaging patients with pancreatic adenocarcinoma. MDCT takes reproducible multi-planar imaging which provides good spatial resolution and attenuation between tumour and

Table 1 Benefits and limitations of pancreatic cancer diagnostic modalities

Diagnostic modalities	Advantages	Limitations
MDCT	Most commonly available	Nephrotoxicity
	Best validated	Radiation exposure
	Cheapest	
MRI	Superior imaging	Expensive
	Depiction of local pancreatic disease	Less available
	Iodine-free and no radiation	Contraindicated with some metal implants
EUS +/- FNA	Safe and less invasive	Less available in some countries
	High sensitivity	Operator dependent
	Able to detect small lesions	Inability to detect distant metastasis
	Able to take histological sample	
PET/CT	Metastatic disease detection	Expensive
	Clarification of equivocal CT findings	Less available
	Monitoring recurrence and response to adjuvant therapy	Radiation and contrast exposure

CT: Computed tomography; MDCT: Multi-detector computed tomography; MRI: Magnetic resonance imaging; EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; PET: Positron emission tomography.

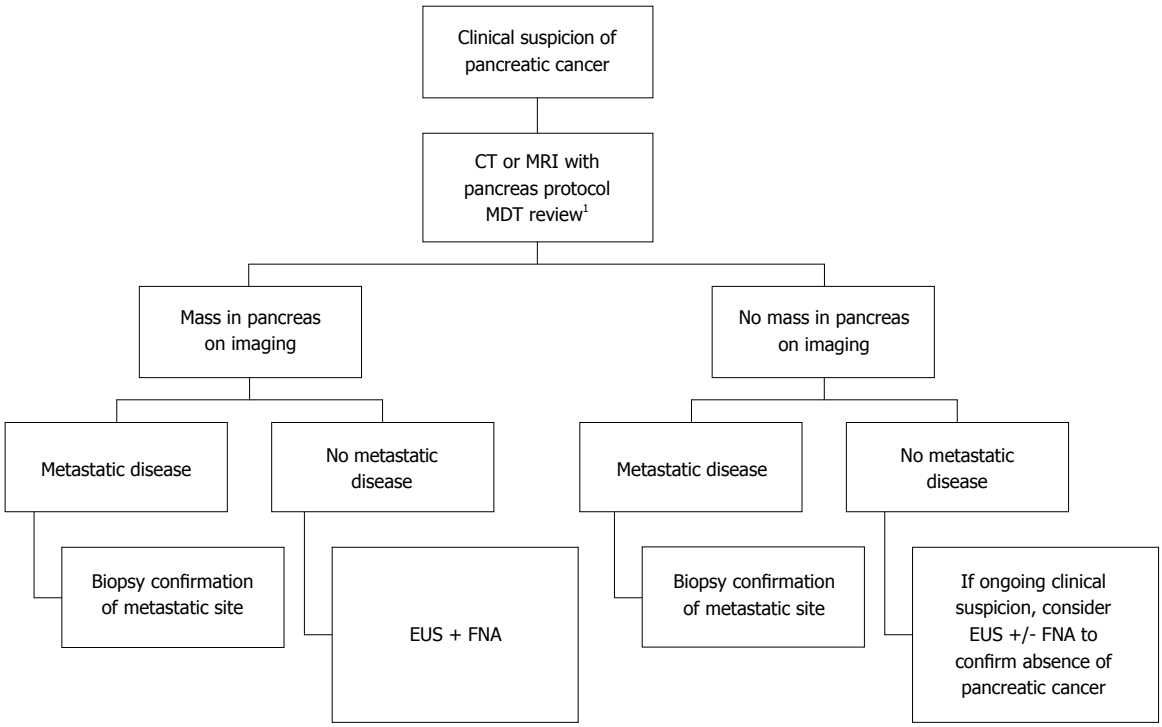

Figure 1 Algorithm for the evaluation of a patient that has clinical suspicion of pancreatic cancer. [1]Multi-disciplinary review should involve a panel including gastroenterologist, surgeon, medical and or radiation oncologist, diagnostic imaging and pathologist. CT: Computed tomography; MDCT: Multi-detector computed tomography; MRI: Magnetic resonance imaging; EUS: Endoscopic ultrasound; FNA: Fine needle aspiration.

background pancreatic parenchyma with wide anatomic coverage, and thus allowing comprehensive examination of local and distant disease in one single section[8].

Numerous international guidelines endorse the use of CT as the initial modality in diagnosis of suspected pancreatic cancer[9,10]. In particular, MDCT is best performed according to a dedicated pancreas protocol[10]. Despite some inter-institutional variability, the standard MDCT pancreas protocol is a helical type scan that takes interval images of 0.5 to 1 sub-millimetres, with two phases: pancreatic parenchymal phase at 40 to 50 seconds and portal venous phase at 65 to 70 seconds. The majority of modern scanners are 128 and 256 slice scanners. It includes the administration of both intravenous high iodine concentrated contrast, injected at a rate of 3 to 5 mL per second and ingestion of neutral oral contrast. The pancreatic phase is described as the intermediate between the arterial and hepatic phase where maximal enhancement of the pancreas is achieved to see the contrast between tumour and pancreatic parenchyma, as well as visualization of the peri-pancreatic arteries and veins[11]. The image is usually reconstructed in the following ways: (1) axial views at 2 to 5 mm thickness; (2) coronal and sagittal views with multi-planar reformats at 2 to 3 mm thickness; and (3) vascular evaluations with maximum intensity projections

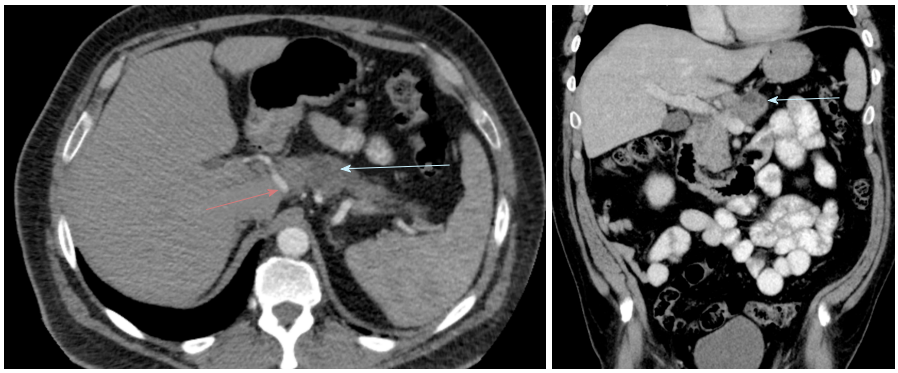

Figure 2 Axial and coronal plane view on computed tomography of a patient with a 2 cm mass in the body of pancreas (blue arrow), abutting splenic artery (red arrow).

or three dimensional (3D) volumetric thick sections.

Pancreatic cancer appears on CT as an ill-defined mass that enhances poorly compared to adjacent normal pancreatic tissue; thus appearing hypodense on arterial phase scans in 75% to 90% of cases, but may become isodense on delayed scans. Findings which may be predictive of pancreatic cancer include, from lowest to highest specificity: ductal dilatation (sensitivity 50% and specificity 78%), hypo-attenuation (sensitivity 75% and specificity 84%), ductal interruption (sensitivity 45% and specificity 82%), distal pancreatic atrophy (sensitivity 45% and specificity 96%), pancreatic contour anomalies (sensitivity 15% and specificity 92%), and common bile duct dilation (sensitivity 5% and specificity 92%)[12]. Figure 2 demonstrates two views on CT imaging of a pancreatic cancer which has abutted into the splenic artery.

When compared with other imaging modalities, CT performs well in the diagnosis of pancreatic cancer. A large meta-analysis comparing various imaging modalities for the diagnosis of pancreatic cancer found a combined sensitivity and specificity of 89% and 90% respectively for CT[13], which was equivalent to MRI. There has been reported improvement in the detection of pancreatic cancer with recent suggestions of sensitivities up to 96% for MDCT, secondary to acquisition of thin collimation images, improved spatial and temporal resolution and use of multi-planar reconstruction and 3D technique[14].

Multi-planar reconstruction on CT is important in tumour staging; providing selective visualization of important arterial and venous structures. This allows for precise visualization of the relationship of the primary tumour to the superior mesenteric artery (SMA), superior mesenteric vein (SMV) and coeliac axis thereby providing an assessment of vascular invasion and resectability. CT is able to distinguish abutment, encasement, narrowing, or occlusion of the portal vein/SMV at the confluence and allow the surgeon to determine if a venous reconstruction is technically feasible[14]. The accuracy of CT in assessment of vascular invasion is not strong, with the most recent studies showing a sensitivity of only 60% and specificity 94% when determining involvement of surrounding vessels[15]. The reason for favouring specificity over sensitivity for vascular invasion is to avoid denying surgery to patients with potentially resectable tumours[16]. Despite these values, consensus statements suggest that preoperative evaluation of surgical resectability be based on CT[17]. CT is also able to provide 3D reconstruction which can be very useful for pre-operative planning by the surgeon.

CT also plays an important role in predicting unresectability. If the tumour surrounds a vessel by more than 180 degrees and occlusion of the SMV/portal vein without surgical options of reconstruction, then it is deemed T4 disease and is unresectable[14]. Recent studies have demonstrated that CT's sensitivity for unresectable disease is between 52% to 91%, and specificities of 92% to 100%[18]. One study also showed that different generations of MDCT equipment did not impact these values[19].

CT also provides the benefit of diagnosing distant intra-abdominal and/or lung metastasis, which is important given that diagnosis of pancreatic cancer is often delayed. Findings of peritoneal carcinomatosis on CT include ascites, peritoneal thickening, contrast enhancement, nodular bowel wall thickening, and soft-tissue infiltration of the omentum[16].

Whilst overall a safe, non-invasive and relatively cheap test to perform, contrast CT is accompanied by the risk of nephrotoxicity from the iodine-contrast agent and as well as involving exposure to radiation. There is also individual variability in getting parenchyma enhancement due to technical factors such as the generation of CT scanner, contrast material volume and concentration and rate of injection, and patient factors such as age, weight and cardiac output[8]. Despite this, most centres still endorse the use of MDCT as the first line modality of choice for diagnosing pancreatic cancer and should not be substituted by other more advanced imaging modalities.

MRI

MRI of the pancreas works by evaluating the speed of the diffusion process by random translational mole-

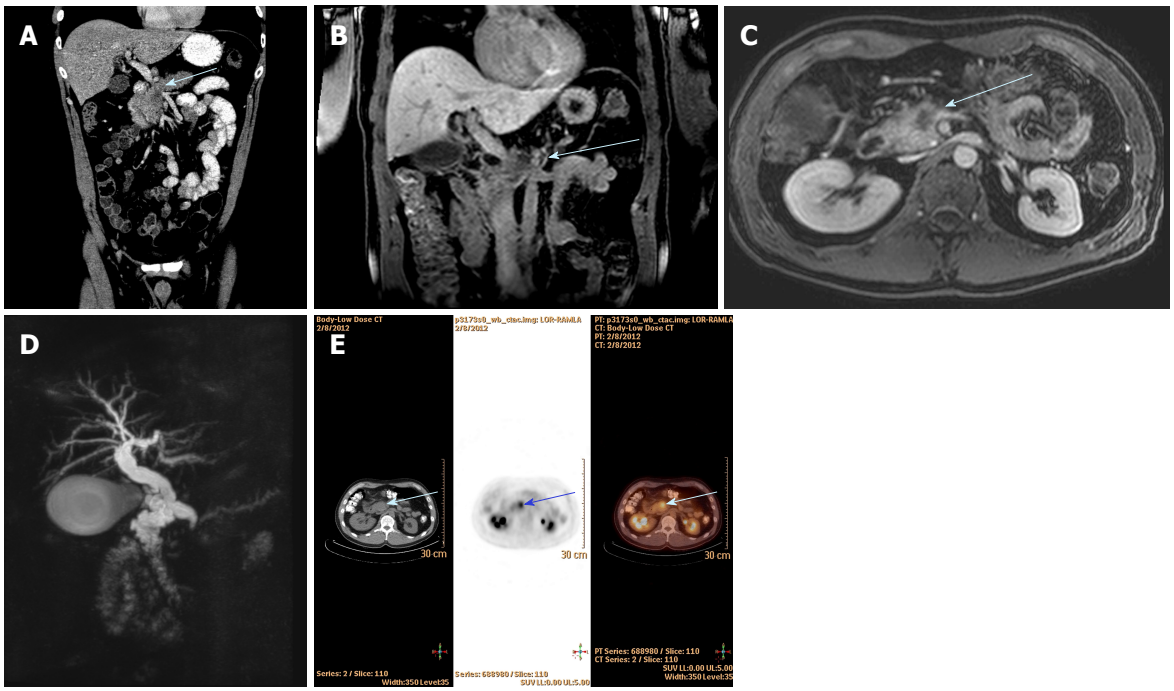

Figure 3 Multimodal imaging techniques utilised for a patient with 2.8 cm head of pancreas cancer (blue arrow) with portal vein and superior mesenteric vein invasion. A: Hypodense mass on coronal view on CT; B: T1-weighted coronal view on MRI; C: T1-weighted axial view on MRI; D: MRCP view with dilated CBD and PD (double duct sign); E: Axial view on PET CT imaging showing marked FDG avidity. CT: Computed tomography; MDCT: Multi-detector computed tomography; MRI: Magnetic resonance imaging; PET: Positron emission tomography; MRCP: Magnetic resonance cholangiopancreatography; FDG: Fluorodeoxyglucose.

cular motion which differs between extracellular and intracellular components of tissue, as well as differences in tissue cellularity and cell density[20]. The pancreas protocol for MRI includes several sequences: T2-weighted single-shot fast spin-echo (SSFSE), T1-weighted in-phase and opposed-phase gradient echo (GRE), T2-weighted fat-suppressed fast spin-echo (FSE), and diffusion-weighted imaging (DWI) all provide an axial plane with less than 6mm thick slices[21]. There is also the option to have pre- and dynamic post- IV contrast administration (gadolinium) 3D T1-weighted fat-suppressed gradient- echo (in pancreatic, portal venous, and equilibrium phases) which provides an axial plane but with the thinnest possible slices of 2 to 3 mm[21]. Pancreatic adenocarcinomas normally appear hypo-intense to normal pancreas on precontrast T1-weighted images and hypointense or isointense on post-contrast T1-weighted images[16], as seen in Figure 3.

MRI theoretically allows tumour detection at an earlier stage by providing a comprehensive analysis of the morphological changes of the pancreas parenchyma, as well as that of the pancreatic duct. Despite this, in meta analyses, MRI has only been shown to be equally sensitive and specific in diagnosing and staging pancreatic cancer as CT; with a combined sensitivity and specificity of 89% and 89% respectively[13]. This is likely due to the difficulty in demonstrating a significant benefit when the sensitivity and specificity of CT are already relatively high. For this reason, MRI is not widely used as the primary imaging modality in most centres due to issues of its cost and availability[9]. Most experts nevertheless acknowledge the added utility of MRI over CT in certain situations; including the main benefit in differentiating iso-attenuating pancreatic lesions and in characterization of indeterminate liver lesions identified at prior CT examinations[9]. MRI is also valuable in patients with impaired renal function or patients with sensitivities to iodinated contrast. Furthermore, other specific situations MRI seems to have an advantage over CT is in differentiating pancreatic tumours from mass-forming pancreatitis, for tumours less than 2 cm, in the presence of hypertrophied pancreatic head or focal fatty infiltration of the parenchyma[22]. In the authors' experience, MRI is often used as a second-line test when there is a high clinical suspicion of pancreatic tumour despite none being visible on CT.

EUS WITH FINE NEEDLE ASPIRATION

EUS is performed under sedation and involves an upper gastrointestinal endoscopic examination with the use of an echoendoscope. The echoendoscope transducer is positioned in the stomach, in direct proximity to the pancreas so that it enables detailed high-resolution imagines of the pancreas and surrounding vessels, lymph nodes and left lobe of the liver. EUS is a safe, well-tolerated procedure and has the added benefit of allowing fine needle aspiration to be performed in order to obtain a cytopathological diagnosis. It is particularly ideal for lesions less than 2 cm or when there is a clinical

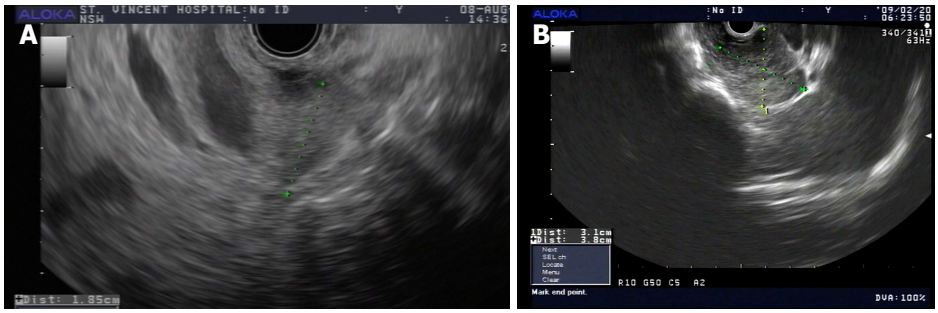

Figure 4 Endoscopic ultrasound images of (A) a small pancreatic adenocarcinoma in the head of the pancreas (1.8 cm) not seen on other modalities; and (B) a 3.1 cm pancreatic adenocarcinoma in the tail of the pancreas.

suspicion of pancreatic cancer but other modalities have failed to identify a mass and for obtaining a confirmatory biopsy. Figure 4 demonstrates the appearance of pancreatic cancers on EUS imagining.

In large meta-analyses EUS with fine needle aspiration (EUS-FNA) was found to be highly accurate in not only diagnosing malignancy but also in diagnosing the correct aetiology for solid pancreatic masses, with sensitivity of over 85% and specificity of 96%[23-26]. Longitudinal studies have also observed a significant increase in diagnostic accuracy over time, likely reflecting an increase in operator proficiency with experience and better visualisation with newer echoendoscopes. The increase in the diagnostic accuracy was seen from 1995-2000 to 2001-2010, with pooled sensitivity of 83.0% increasing to 87.8%, while the pooled specificity remained high at 96.6% and 95.6%[23]. EUS is also used as a reliable tool for local staging, as studies have shown a sensitivity and specificity of 72% and 90% respectively for T1-2 staging, 90% and 72% respectively for T3-T4 staging, and 87% and 92% respective for vascular invasion[27].

The evidence suggests that EUS may have distinct advantages in pancreatic cancer diagnosis when compared with other modalities. Comparative studies with CT have demonstrated the superiority of EUS in primary tumour detection and staging with the absence of a focal mass lesion on EUS reliably excluding pancreatic cancer irrespective of clinical presentation with a negative predictive value of 100%[28]. It has also been shown that the diagnostic accuracy of EUS when no identifiable mass was found on spiral CT was 92%[29]. In a recent meta-analysis, CT scan showed lower sensitivity than EUS for nodal staging (24% *vs* 58%) and vascular invasion (58% *vs* 86%); however, the specificities for nodal staging (88% *vs* 85%) and vascular invasion (95% *vs* 93%) were comparable in studies where both imaging techniques were performed[30]. EUS has its greatest benefit over CT and MRI for small pancreatic neoplasms (less than 2 cm), having a sensitivity of 94% compared with 69% for MDCT and 83% for MRI[31].

Still, perhaps the clearest demonstration of the benefits of EUS-FNA is its ability to obtain a tissue biopsy. Large meta-analyses have demonstrated superiority of EUS-FNA, with pooled sensitivity of more than 85% to 92% and pooled specificity of 94% to 100% in the diagnosis of pancreatic lesion[23-25,28]. EUS is also shown to be the best imaging modality for detecting vascular (especially portal vein) invasion, with a reported accuracy of 82%, compared with CT's accuracy of 79%[29]. The overall complication rate of EUS-FNA is very low 0.85%[32] (including infection, self-limiting pancreatitis) and if the tumour is in the head of pancreas, the needle tract will be part of the resected specimen thus minimising the risk of tumour seeding. Tumour seeding during EUS-FNA is a rare but important complication to be considered, with only a few case reports ever documented[33,34]. Apart from this, other major complications such as perforation, are extremely rare with a risk of 1:2500[24].

Fine needle aspiration technique

Different techniques in retrieving samples have been investigated for EUS including "fanning", "slow pull" and the "wet suction" technique (WEST). Randomised trials comparing "fanning", which involves sampling multiple areas within a lesion with each pass, with standard technique found that fanning was superior and fewer passes were required to establish the diagnosis[35]. There was however no difference in diagnostic accuracy, technical failure or complication rates[35]. As for the "slow pull" technique, where minimum negative pressure is provided by removing the stylet from the needle slowly and continuously, lower scores for contamination with blood were found, with a higher sensitivity of diagnosis of malignancy[36]. Lastly, the WEST technique, which involves flushing the needle with 5 mL of saline solution to replace the column of air within the lumen of needle to improve the quality of aspirate, also resulted in significantly better cellularity and specimen adequacy in cell blocks and specimen adequacy, but had no difference in the amount of blood contamination[37].

On-site cytopathologist

The presence of an on-site cytopathologist has a beneficial effect on the diagnostic yield of EUS FNA, by significantly lowering the number of inadequate samples, and increasing the diagnostic sensitivity and overall accuracy for malignancy[38,39]. Studies demonstrated the cost effectiveness of having an on-site cytopathologist where the same accuracy of 87% was achieved with

only 2.1 passes, compared to the 4 passes needed when real-time evaluation of specimens was not available[40].

Contrast-enhanced EUS

Contrast-enhanced EUS (CE-EUS) is a technique in which during the EUS, a second-generation low mechanical index microbubble ultrasound agent (UCA) is injected peripherally. Due to its small size (2 to 10 μm), it detects very slow flow and provides real time perfusion imaging without the burden of Doppler-related artefacts[41].

Observational studies have demonstrated more accurate characterization of solid pancreatic lesions seen on EUS by estimating their vascularity after injecting a contrast agent. It was also found that a hyper-enhancing lesion on CE-EUS was highly specific (more than 98%) for excluding adenocarcinoma, while a hypo-enhancing and hypo-echoic lesion was highly sensitive (more than 86%) for adenocarcinoma[41]. It also helps differentiate between a pancreatic adenocarcinoma (because of lower uptake of contrast, or hypoenhancement) and neuroendocrine tumours (NET), lymphoma, metastasis, and pseudo-papillary tumours that mimic cancer but show hyper-enhancement on CE-EUS. CE-EUS is beneficial in confirming that small pancreatic lesions are NET (hypervascular lesions with early arterial enhancement), characterisation of a mural nodule and malignant transformation of intrapapillary mucinous neoplasms[42] and in providing further information on solid masses in patients with chronic pancreatitis. There is also potential to utilise CE-EUS for targeted EUS FNA to improve the accuracy of biopsy by avoiding necrotic tissue and by selecting the most adequate target. There are minimal studies available assessing this and so this poses a potential topic for future research.

Despite these findings, CE-EUS is not yet widespread in all centres around the world. CE-EUS should not be used in patients with unstable angina and there is a small chance of an allergic reaction to the contrast.

EUS fine needle aspiration versus fine needle biopsy

There has been recent research looking into techniques to increase the amount of tissue acquisition to improve the diagnostic accuracy of samples. Fine-needle biopsy needles (EUS-FNB) have been designed in order to allow core biopsies with preserved architecture which would enable histological analysis, by shearing tissue from the target lesion. Initially, 19-gauge calibre needles were utilised but the mechanical friction caused by the torqued echoendoscope limited its use for evaluating pancreatic head masses[43]. Studies assessing Trucut needles showed that there was no significant difference between the diagnostic accuracy of 19-gauge Trucut needle and EUS-FNA needle, with a reported accuracy of 78% and 89% in one study[44]. However, there were more technical issues experienced with Trucut needle.

Newer 19-gauge, 22-gauge 25-gauge EUS needles with reverse bevel technology (Pro-core, Cook Medical; Winston Salem, NC, United States), Franseen type needles (Acquire, Boston Scientific, Marlborough, MA, United States) and fork-tip needles (Shark Core, Medtronic, Minneapolis, MN, United States) were developed to overcome the technical issues which allowed acceptable histological core samples and cytology aspirates, with diagnostic accuracies of more than 90%[45].

A study comparing 22-gauge FNA and FNB needles showed diagnostic cytologic specimens in 89.3% of patients and histologic specimens in 80% of patients with solid pancreatic mass lesions[43]. Similarly, a recent meta-analysis showed no significant difference in diagnostic adequacy (75.2% *vs* 89.0%), or diagnostic accuracy (85.8% *vs* 86.2%) between biopsy and aspiration needles[46]. Most recently, a small retrospective study showed better results with a 25-gauge core biopsy needle reporting a combined cytological and histologic sensitivities of 85%, specificities of 100% and accuracies of 86% with a single pass and minimal complications[47].

If the FNB needle design can be further improved and be routinely shown to provide diagnostic yields high enough to eliminate the need for on-site cytopathological evaluation, then this could also lead to a significant reduction in the costs of pancreatic cancer.

EUS elastography

EUS elastography measures tissue elasticity in real time using a dedicated software during an EUS examination. Elasticity is depicted using a colour map, where hard tissue is shown in dark blue, medium hard tissue in cyan, tissue with intermediate hardness in green, medium soft tissue in yellow and soft tissue as red. Pancreatic malignancy appears as a heterogenous blue predominant mass, whereas normal pancreas appear as homogeneous green and inflammatory pancreatic masses have a heterogeneous, green-predominant appearance[48]. The sensitivity and specificity of EUS elastography to differentiate benign from malignant pancreatic lesions has been reported as 92.3% and 80.0%, respectively, compared to 92.3% and 68.9%, respectively, for the conventional EUS B-mode images[49]. Elastography is mainly used in Europe. It does have limitations, as colour pattern provides a subjective determination and has intra-observer and inter-observer variability. Other studies reviewing elastography has not been strong and so more research is required to make conclusions regarding its benefits.

While elastography and CE-EUS provide additional benefits to standard EUS, the combination of elastography and CE-EUS does not significantly increase the diagnostic accuracy of either of the techniques performed alone[50]. Each modality has its benefits in selected cases.

PET

PET with F-18-fluorodeoxyglucose (18FDG) has no additional benefit in diagnosis of pancreatic cancer. However, a more recent triple phase enhanced 18FDG-

PET has been combined with CT to produce one fusion image, as seen in Figure 3. At this point in time, experts do not recommend PET/CT as a substitute for high-quality contrast-enhanced CT because its role is still being established[9]. Despite this, the research has been promising with the use of PET/CT for staging. A meta-analysis has shown that the pooled sensitivity of PET in diagnosis, in evaluating N staging and in liver metastasis were 91%, 64% and 67% respectively; and the corresponding specificities were 81%, 81% and 96% respectively[51]. These values are higher than CT alone. However, as a diagnostic tool, PET/CT performs similarly to CT alone and hence adds no benefit over the current primary diagnostic tools in diagnosing pancreatic cancer[52].

Though the value of PET/CT alone for diagnosing pancreatic cancer has not been shown to be better, some studies have investigated its combined use with other techniques. A meta-analysis has shown that the combination of PET/CT plus endoscopic ultrasonography is useful for suspected pancreatic cancer because of the high sensitivity of PET/CT and the high specificity of endoscopic ultrasonography[53]. While initially it was hoped that PET/CT will be able to differentiate between mass-forming chronic pancreatitis and pancreatic cancer, this is not the case due to considerable overlap between the Standardised Uptake Value (SUVmax) values of these two diseases[54]. FDG PET/CT has been shown to provide additional benefit in detecting distant metastasis, particularly bone metastasis[55].

PET/CT shows promising role in assessing tumour response to chemo-radiation therapy with the measurement of the change in SUV pre- and post- treatment, which could potentially serve as a trial for preoperative neoadjuvant therapies[56,57].

In conclusion, at the present stage, PET/CT has no role in routine diagnosis of pancreatic cancer but can be used as an adjuvant modality in selected cases.

ULTRASOUND AND ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

The pancreas is a retroperitoneal organ and hence the sensitivity of transabdominal ultrasound is poor in detecting pancreatic cancer and is not used in diagnosis or staging of pancreatic cancer[58]. The sensitivity according to studies vary between 48% and 89% with lower specificity and accuracy, with variation in these rates with the size of the tumour and operator's level of experience[59].

Given the excellent modern imaging, Endoscopic retrograde cholangiopancreatography (ERCP) plays a less prominent role in diagnosis of pancreatic cancer[60], and is mainly used as a therapeutic modality due to potential complications such as pancreatitis and perforation[61]. ERCP remains an important modality to provide biliary drainage in obstructing head of the pancreas cancer and can provide biliary and pancreatic duct brushing cytology in patients with invasive pancreatic cancer[62]. Pancreatogram obtained during the ERCP can show pancreatic duct stenosis, obstruction, narrowing and abnormal branching of the main pancreatic duct, obstruction and encasement of the common bile duct. There are few studies that looked at ways to attain cytological samples during ERCP through the use of an endoscopic naso-pancreatic drainage (ENPD) tube which is placed in the main pancreatic duct to collect pancreatic juice repeatedly - a technique known as serial pancreatic-juice aspiration cytologic examination or "SPACE"[63]. Only small-scale studies have examined the use of this technique with relatively promising results[63-65], but more research is required prior to recommendation of its use.

BIOMARKERS

At present, there is no reliable diagnostic biomarker for pancreatic cancer. A number of potential tumour markers have been evaluated, but the most extensively studied for diagnosing pancreatic cancer is carbohydrate antigen 19-9 (CA 19-9). CA 19-9 is however expressed and shed in a number of pancreatic and hepatobiliary diseases, as well as other malignancies. CA 19-9 may be falsely positive in cases of biliary infection, inflammation, or obstruction (regardless of aetiology) and does not necessarily indicate cancer or advanced disease[66]. For these reasons, it performs poorly as a screening tool, with a low positive predictive value of 0.5% to 0.9%[66]. However, CA 19-9 does have a role as a prognostic marker and for monitoring for recurrence after resection[9]. It performs better in symptomatic patients, with a sensitivity and specificity of 79% to 81% and 82% to 90% respectively for the diagnosis of pancreatic cancer in this setting[67,68]; with a CA 19-9 serum level of 100 U/mL suggestive of unresectability or metastatic disease[67]. As well as its issues with specificity, CA 19-9 sensitivity is also suboptimal; for example, CA 19-9 may be undetectable in Lewis antigen-negative individuals and hence can be negative in patients with advanced cancer.

There are a number of potential pancreatic cancer biomarkers that are being investigated. in particular, serum macrophage inhibitory cytokine 1 (MIC-1) is a promising biomarker whose levels in the serum are typically elevated in patients with pancreatic adenocarcinoma. Though performing sub-optimally when used on its own, it has been shown to produce improved diagnostic accuracy when combined with CA 19-9[69]. Other studies have also studied single research biomarkers such as CECAM-1, Span-1, DUPAN-2, Alpha4GnT, PAM4, and combined biomarkers with CEA, CA 19-9, and CA 242[70,71], but none demonstrating sufficient diagnostic accuracy to be used as a screening test at this stage.

More recently, a combined panel of protein and microRNAs serum exome for pancreatic cancer have emerged as potential diagnostic tools with improved sensitivities and specificities but have yet to have testing

within larger cohorts[72]. There has also been early research reviewing the use of inorganic nanomaterials such as gold and carbon nanotubes which can be targeted towards specific pancreatic cancer cells, in early detection and diagnosis[73].

SCREENING PROGRAMS

Pancreatic cancer screening is not feasible in the general population due to the low incidence of pancreatic cancer and lack of a cheap, easy and accurate screening test. However, approximately 5% to 10% of pancreatic cancers are due to a known genetic mutation and/or have familial aggregation. As pancreatic cancer patients become symptomatic later in the course of the disease, early detection programs have been developed in asymptomatic people at high risk of pancreatic cancer (individuals with a 5% or more lifetime risk of pancreatic cancer). The high-risk groups include familial pancreatic cancer (members of a family with at least 2 first degree relatives with pancreatic cancer) and inherited pancreatic syndromes including Peutz-Jeghers syndrome (lifetime risk of pancreatic cancer 36%), familial atypical multiple mole melanoma syndrome (lifetime risk 17%), hereditary pancreatitis (lifetime risk 49%), PALB2 mutation, known BRCA2 carrier with a first degree with pancreatic cancer, Lynch syndrome with a first degree with pancreatic cancer[74]. In these high risk groups, the International Cancer of the Pancreas (CAPS) Consortium recommends starting screening at age 50, with yearly surveillance if no pancreatic lesions are detected at baseline assessment[75]. EUS and MRI are the imaging modalities of choice for screening as they have sufficient sensitivities and specificities to detect small lesions (or early cancer) and do not carry the risks of radiation exposure. In these high risk groups, the overall yield for detecting premalignant and malignant lesions using EUS is 20% and using MRI/MRCP is 14%[76]. EUS performs better for small solid lesions and MRI for cystic lesions. The current data from prospective observational studies indicate that the diagnostic yield of neoplastic pancreatic lesions varies significantly, depending if pre-cancerous lesions (such as cysts, branch duct IPMN, main duct IPMN) are included or not in the analysis, the screening modality and the target population, being between 5% to 43%, whereas the detection rate for pancreatic cancer is 2%. These data are consistent with the findings from a recent systematic review of 542 high-risk individuals screened[76]. Currently, screening programs are recommended to be conducted only by experienced clinicians in a research setting with prospective data collection and close international collaboration.

PERILS, PITFALLS AND SUBTLETIES IN THE DIAGNOSIS OF PANCREATIC CANCER

With the use of multimodal imaging techniques and tissue acquisition as described above, a definitive diagnosis of pancreatic cancer can be made in the majority of patients when suspicion arises. Nevertheless, there are a number of situations where diagnostic findings are difficult to distinguish from other benign conditions affecting the pancreas. Accurate diagnosis in these settings is crucial given the disparate therapeutic implications, and generally relies on identifying and recognising radiological or endoscopic subtleties, emphasising the importance of close collaboration with expert centres.

Focal chronic pancreatitis

Focal chronic pancreatitis is a common mimicker of pancreatic cancer. It can form a focal mass and subsequently can cause pancreatic and biliary ductal obstruction which may be indistinguishable in appearance to that caused by ductal adenocarcinoma[14]. Standard imaging techniques including CT, MRI can be inconclusive to distinguish the two in selected cases. Depending on the degree of inflammation and fibrosis, CE-EUS and elastography could help distinguish between pancreatic adenocarcinoma and pseudotumoural chronic pancreatitis. In these cases, EUS guided biopsy is important and very close monitoring is recommended in biopsy negative cases.

Autoimmune pancreatitis

Autoimmune pancreatitis clinically can present in a similar fashion to pancreatic cancer; both most often occurring in older persons typically aged over 60 years and presenting as painless jaundice, new-onset diabetes mellitus, and raised levels of serum tumour markers[77]. Serum IgG4 is frequently increased in autoimmune pancreatitis, but occasionally can be mildly raised in 4% to 7% of pancreatic cancers[78]. However, the specificity of IgG4 to autoimmune pancreatitis is strong, especially when the serum IgG4 level is significantly raised to at least twice the upper limit of normal[79]. Typical CT findings for autoimmune pancreatitis include a smooth, diffusely enlarged homogenous gland with delayed enhancement and capsule-like rim[78] as seen in Figure 5. However, autoimmune pancreatitis can also appear as a mass on CT if there is focal involvement[14]. PET/CT with 18FDG has been shown to help differentiate these two diseases, with diffuse pancreatic uptake of FDG and concomitant uptake by salivary glands more suggestive of autoimmune pancreatitis[80]. Histopathologic evidence from a biopsy via EUS-FNB can produce the most definitive confirmation by demonstrating typical features of autoimmune pancreatitis such as lympho-plasmacytic sclerosing pancreatitis, abundant IgG4 positive cells, idiopathic duct centric pancreatitis and/or granulocyte epithelial lesion in the pancreatic duct[81]. IgG4 staining of the ampulla biopsy is also suggestive of autoimmune pancreatitis. Finally, autoimmune pancreatitis is usually sensitive to treatment with steroids, so a positive therapeutic trial can be helpful in excluding pancreatic cancer in equivocal cases[77].

Solid pseudopapillary neoplasm of the pancreas

Solid pseudopapillary neoplasm (SPN) is a rare indolent

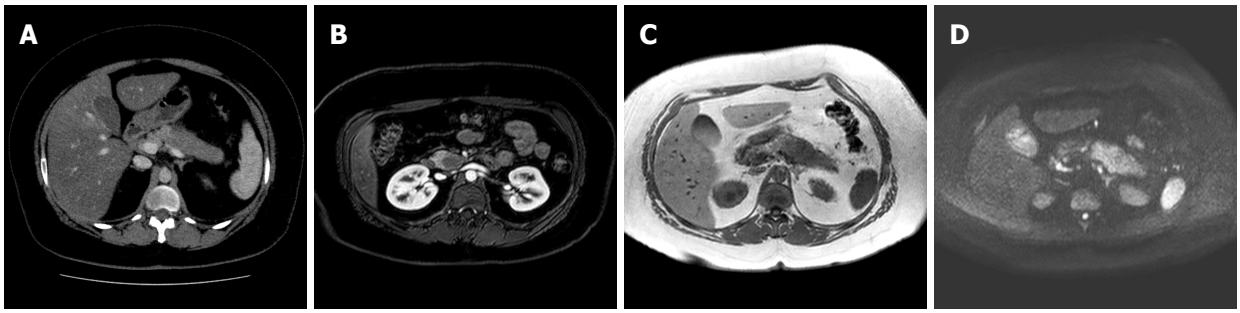

Figure 5 Multimodal imaging techniques demonstrating autoimmune pancreatitis in a patient. A: Diffuse enlargement "sausage shape" of the tail axial view on CT; B: Head of the pancreas axial view in arterial phase on MRI; C: Tail of the pancreas T1-weighted axial view on MRI; D: Homogenous restricted diffusion on DWI axial view MRI. CT: Computed tomography; MRI: Magnetic resonance imaging; DWI: Diffusion-weighted imaging.

neoplasm that has a low malignant potential and can be cured with resection but can be difficult to differentiate radiologically from pancreatic adenocarcinoma[82]. SPN usually occurs in younger women and is located in the tail of the pancreas. MRI is better than CT in detecting this tumour, with typical findings of an encapsulated mass with solid and cystic components, as well as haemorrhage without an obvious internal septum[81]. The typical EUS appearance is of mixed solid cystic lesion with a median tumour size of 4.2 cm but sometimes it can present as a solid mass. The diagnostic yield of CT alone is 23%, EUS is 41% with a combined diagnostic yield of 52%. EUS FNA significantly increased the diagnostic yield to 82%[83].

It is also important to not incorrectly diagnose adenocarcinoma in patients with SPN as there is a 5-year survival rate of 96.9% post resection for SPN regardless of the size of the tumour[82].

Annular pancreas

Annular pancreas is a rare congenital migratory abnormality, with a reported incidence rate of up to 1 in 1000, and is due to incomplete rotation of the ventral anlage around the duodenum that leads to the pancreas encircling the second part of the duodenum[84]. These patients are asymptomatic and it is usually an incidental finding on CT or MRI. An experienced radiologist should be able to distinguish an annular pancreas from a pancreatic mass, as a normal enhancing pancreas and pancreatic duct encircling the second part of the duodenum.

Pancreatic lipomatosis

Sometimes fatty replacement of the anterior portion of the pancreatic head is seen in diabetes, obese or elderly people. This can mimic a hypodense mass on CT, however an MRI with in and out phases can exclude the presence of a true mass by showing the presence of intracellular fat[85].

PERSPECTIVES AND FUTURE DIRECTIONS

Future research should focus on improving outcomes in pancreatic cancer through the development of new diagnostic techniques with higher diagnostic accuracy. We should also aim to develop better tools to assess risk for developing cancer thereby facilitating better targeting of screening programs and better selection of patients for surgery.

Apart from those already discussed, examples of other promising novel diagnostic techniques that are under research include needle based confocal laser endomicroscopy (n-CLE), where a probe is passed through a 19-gauge EUS needle for real-time visualization of the tissue at the microscopic level in the pancreatic cysts, thus providing an optical biopsy[86]. Similarly, probe based confocal laser endomicroscopy (p-CLE) can be used during an ERCP for indeterminate pancreato-biliary stricture[87].

An ideal FNB needle design has not been found yet. A recent study showed that fork tip needle had a higher histologic yield than bevel needle but further studies are needed to compare all types of FNB needles[88]. Obtaining adequate histological samples of the tumour during the EUS is very attractive, as it can lead to enough samples for DNA extraction, comprehensive whole exome sequencing and next generation sequencing (NGS) of the pancreatic tumour. A large amount of DNA will facilitate preoperative genomic profiling and chemotherapy testing and will play a role in individualised cancer treatment.

Mutation of the KRAS oncogene is present in 75% to 95% of pancreatic cancer tissues. Combining EUS-FNA cytology with *KRAS* mutation analysis on the biopsy material can increase the pancreatic cancer accuracy from 85% to 94%[89]. This study shows promising results particularly as EUS-FNB needles will continue to improve and more material is obtained during the biopsy.

Detection of *TP53* mutations in secretin-stimulated pancreatic juice samples collected from the duodenum of the patients with high grade dysplasia and pancreatic cancer[90] opens a new area of future research in diagnosis and potential screening for early pancreatic cancer.

EUS guided sampling of portal venous blood for circulating tumour cells may enhance the ability to detect occult metastatic disease, allowing improved patient selection for surgery[91]. Advances in these fields will be most beneficial in improving the outcomes of patients with pancreatic cancer.

Whole genome sequencing of pancreatic adenocarcinoma has found chromosomal rearrangements leading to gene disruption and new candidate drivers in pancreatic carcinogenesis[92]. The development of focus panel testing for pancreatic cancer is already underway which will potentially allow tumour subtyping, and may aid in the development of tumour specific targeted therapies[93]. These and other advances in genetic understanding, including the identification of several microRNAs involved in regulation of aberrant cell replication, render them potential biomarkers for diagnosis and prognosis[94].

CONCLUSION

While the early diagnosis of pancreatic cancer remains challenging, improvements in diagnostic technology and methodologies in the last decade will hopefully translate into improved outcomes. Screening of high-risk individuals using EUS and/or MRI is recommended and shows promise in early detection. In patients with suspected pancreatic cancer we propose the use of CT or MRI as first-line investigations, with the choice between the two being determined by cost, availability and local expertise. Such cross-sectional imaging modalities remain the gold standard for staging, both of the primary lesion and detection of distal metastases. EUS has become a powerful diagnostic modality and should be used in adjunct, being superior in the detection of small lesions and having the ability to obtain a tissue diagnosis. While research is ongoing, at present there is no role for the use of any routine biomarker in the diagnosis of pancreatic cancer. Atypical cases can occur and differentiation of malignant from benign pancreatic lesions can be challenging; in these cases, opinion from a radiologist with pancreato-biliary expertise should be sought.

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