PANCREATIC CANCER DIAGNOSIS AND SCREENING

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Abstract

Pancreatic cancer is uncommon, but is projected to become the second leading cause of cancer-related death by 2030. The dismal five year survival of 5% reflects the advanced stage of the disease at presentation, at which time surgery is not possible. The establishment of clinical and pathological diagnosis currently relies on dedicated 'pancreatic protocol' CT, MRI/cholangiopancreatography, endoscopic ultrasound and guided fine needle aspiration. Given surgical resection of early stage cancer is curative at least in some cases, the concept of screening high-risk individuals to detect the cancer at its earliest stage has been evaluated over the last 10 years. Although the advances in imaging modalities, particularly those without radiation exposure, such as endoscopic ultrasound and MRI have made screening programs safe and feasible, studies demonstrating the impact of these programs on survival outcomes are lacking. Thus, screening of high-risk individuals is not ready for widespread clinical practice and should be conducted by clinicians who have expertise in endoscopic ultrasound for screening of high-risk individuals in a research setting with prospective data collection.

Despite the reduction in incidence of all other cancers in recent years, there has been an increase in pancreatic cancer incidence over the last three decades and it is projected to be the second most common cause of cancer death by 2030.[1] Improvement of survival relies heavily on early detection, with surgical resection perceived as the only curative option.[2] Unfortunately, only 20% of patients are suitable for surgery at diagnosis.[3] Diagnosis predominantly requires imaging techniques (CT, MRI/cholangiopancreatography [MRCP], endoscopic ultrasound [EUS]) and tissue acquisition. One strategy for improving outcomes in patients with pancreatic cancer is to develop effective screening protocols to identify more patients at an earlier stage, by identifying highly specific biomarkers or 'high-risk' individuals for pancreatic cancer. Unfortunately, thus far, there are no reliable tumour markers or biomarkers for the early detection of pancreatic cancer.[4] This review focuses on diagnosis and screening of pancreatic cancer.

Diagnosis

Clinical manifestations

The majority of patients with pancreatic cancer present late as they are often asymptomatic in the early stage of their disease. The most common symptoms at diagnosis are either painless jaundice or vague epigastric pain radiating to the back. This is because over two thirds of pancreatic cancers are located in the head of the pancreas and cause obstruction of the biliary tract.[5] Other non-specific complaints include anorexia, weight loss, lethargy and change in bowel habit. In advanced disease, symptoms of gastric outlet obstruction (post-prandial nausea and vomiting) can occur secondary to duodenal stricture caused by direct tumour invasion, suggesting that clinical manifestations can be an indicator of disease staging. Abdominal pain and weight loss are more frequently found in patients with later stages of disease.[6]

Investigations

Although a number of conventional imaging modalities can be used for the work-up of pancreatic cancer (table 1),[7] contrast 'pancreatic protocol' multi-detector row computed tomography (MDCT) is the best initial imaging modality for both the diagnosis and staging of patients with suspected pancreatic cancer.[8] MRI with MRCP has similar sensitivity and specificity in detection of pancreatic cancer and can be used as an alternative to MDCT depending on the local expertise and availability. MRI is most useful in cases where CT fails to show a mass lesion within the pancreas, or tumours are suspected to be smaller than 1cm, either in the pancreas or liver.[9] For pancreatic lesions less than 2cm, EUS has a sensitivity of 93%, which is significantly greater than that from MDCT (53%) and MRI (67%) (table 2),[10-17] and has a major role in patients who have had cross sectional imaging but were still unable to definitively rule out pancreatic lesions. The sensitivity

of trans-abdominal ultrasound is poor and it is therefore not used.[18,19] The role of positron emission tomography with CT (PET/CT) in the work-up of pancreatic cancer remains unclear. In a recent prospective study of 56 patients, PET/CT altered management in 16% of patients due to detection of metastases that was not identified by other imaging modalities.[20] Given its relatively small impact in the overall management, PET/CT is not routinely recommended in the work-up of pancreatic cancer.

Serum carbohydrate antigen sialyl Lewis, also known as Ca19-9, greater than 1000U/ml in conjunction with a pancreatic mass is highly diagnostic of pancreatic cancer. However, Ca19-9 is not specific to pancreatic cancer and can be markedly increased in biliary obstruction. The overall sensitivity and specificity of Ca19-9 for predicting the presence of pancreatic cancer in a patient with a pancreatic mass, are both 80%.[21] A normal Ca19-9 result does not exclude pancreatic cancer.[22] Monitoring serum Ca19-9 level is also useful in assessing the therapeutic response to various types of treatment in patients with pancreatic cancer. In patients undergoing surgical resection, postoperative decrease to less than 200 U/mL has been shown to be a strong predictor of survival.[23] In patients with locally advanced pancreatic cancer undergoing neoadjuvant chemoradiotherapy, a level less than 90 U/mL is associated with increased overall survival with the possibility of surgical resection.[24]

EUS-FNA has become the preferred technique for establishing tissue diagnosis, with sensitivity of 85% and specificity 98%.[25] It is a safe procedure with complication rates of approximately 1%,[26] and the risk of tumour seeding is significantly lower than that of the percutaneous approach.[27] Contrast enhancement and elastography are adjunctive techniques during EUS evaluation, as both can increase the sensitivity and accuracy of pancreatic cancer detection and help target the best area for FNA.[28,29]

***Table 1**: Summary of imaging modalities for detection of pancreatic cancer.*

Imaging modality	Sensitivity	Specificity	Advantages	Disadvantages
Trans-abdominal ultrasound	50-90%	98%	Minimally invasive, inexpensive	Unreliable for exclusion
MD CT	75-100%	70-100	Good assessment of vascular invasion and distant metastases	Less sensitive for lesions ≤2cm
MRI/MRCP	84-100%	88%	Better ductal assessment; vascular invasion	
EUS	Approaching 100%	95%	EUS FNA; high accuracy even with lesions < 2cm; local staging	Invasive, limited imaging range

***Table 2**: Diagnostic accuracy of EUS, CT and MRI for identifying pancreatic mass.*

Publications	Sample size	MRI	CT	EUS	P-value
Palazzo 1993	64		69%	96%	<0.05
Yasuda 1993	29		72%	100%	<0.05
Muller 1994	49	83%	69%	94%	<0.05 (EUS vs CT) NS (EUS vs MRI)
Nakaizumi 1995	232		65%	94%	<0.05
Gress 1999	81		74%	100%	<0.05
Mertz 2000	35		53%	93%	<0.05
DeWitt 2004	80		86%	98%	<0.05
Borbath 2005	59	88%		98%	NS

NS – non significant

Staging of pancreatic cancer

Accurate disease staging is crucial to the management of pancreatic cancer, as surgical resection carries significant morbidities and mortality. MDCT is the imaging modality of choice for the assessment of vascular involvement and distant metastasis.[30-32] If MDCT is not available, MRI/MRCP can be considered an appropriate alternative.[33] When available, EUS should also be used for tumour (T) and nodal (N) staging, especially as an adjunct examination during EUS guided biopsy. A recent meta-analysis showed that for resectability, EUS has a similar sensitivity (87 vs 90%) and higher specificity (89 vs 69%) compared to MDCT,[34] but is superior to CT for detection of tumour invasion at the portal vein confluence (table 3).[14,16,35-37] Furthermore, EUS has a higher sensitivity over MDCT for detecting (and sampling) coeliac lymph nodes and small ascites.[38,39] EUS however, has limited ultrasound penetration range and cannot detect distant metastatic disease.[40] Therefore, EUS and MDCT have complementary roles in the staging of pancreatic cancer.

***Table 3**: Accuracy of EUS/CT/MRI in staging pancreatic cancer.*

Publications	Sample size	MRI	CT	EUS	P-value
Gress 1999	81		60%	93%	<0.001
Ahmad 2000	63	77%		69%	NA
Ramsay 2004	27	83%	76%	63%	NS
Soriano 2004	62	75%	83%	67%	NS
DeWitt 2004	53		77%	77%	NS

NS – non-significant

Screening for pancreatic cancer

Most patients with pancreatic cancer remain asymptomatic until the tumour has grown to an unresectable stage.[3] Given the five-year survival of patients with resected tumours less than 1cm in size is as high as 78%,[41,42] the most logical way to improve survival is via the identification of early disease or precursor lesions by screening asymptomatic individuals. There are three known histologically well-defined precursor lesions involved in pancreatic carcinogenesis called pancreatic intraepithelial neoplasms (PanINs), intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms.[43] A recent study indicated that there was a 10 year interval between the initial mutation and the birth of the first pancreatic cancer founder cell, and another six years for the development of the clone with metastatic potential.[44]

Currently, a population based screening program is not feasible due to the low incidence of pancreatic cancer (approx. 11:100,000 in Australia) and the lack of simple, safe, accurate, inexpensive and non-invasive diagnostic tests for early lesions.[45] As proposed by the International Cancer of the Pancreas Consortium (CAPS) however, screening individuals with a greater than 5% lifetime risk or five-fold increased relative risk of developing pancreatic cancer (i.e. high-risk individuals) may be cost-effective and is under evaluation.[46]

A number of inherited and acquired conditions significantly increase the risk of pancreatic cancer (table 4 and 5). Up to 10% of pancreatic cancer results from a genetic susceptibility and/or familial aggregation.[47] Although they are rare, Peutz-Jeghers syndrome (PJs), hereditary chronic pancreatitis and familial pancreatic cancer syndrome (FPC) are the three conditions that subject patients and their first-degree relatives to the highest risk of developing pancreatic cancer (table 4) (8-60% lifetime risk). FPC is characterised by two or more first-degree relatives with pancreatic cancer in the absence of a known cancer syndrome, and thus, those with two or more relatives with pancreatic cancer (with at least one being a first degree relative) should be considered for screening.[46] Although there is a higher prevalence of patients with Lynch syndrome and hereditary breast-ovarian cancer syndrome, the lifetime risk of developing pancreatic cancer with these syndromes is only approximately 5%.[48]

***Table 4**: Hereditary conditions with sufficiently high life-time risk of pancreatic cancer warrant screening and surveillance.*

Condition	Gene	Pattern	Prevalence	Relative risk	Lifetime risk
Peutz Jeghers syndrome	STK11, LKB1	Autosomal dominant	1:100000	132	30-60%
Hereditary chronic pancreatitis	PRSS1	Autosomal dominant	0.3:100000	50-70	40%
Familial atypical multiple mole melanoma syndrome	CDKN2A, p16-Leiden	Autosomal dominant	unknown	20-34	17%
Familial pancreatic cancer syndrome - 3 or more FDR - 2 FDR	PALLD, BRCA2, CDKN2a, PALB-2, FANC-G, FANC-C	Mostly autosomal dominant	unknown	32-48 8-28	16-23% 3-8%
Hereditary breast and ovarian cancer syndrome	BRCA2	Autosomal dominant	1:400-800*	5-10	5%
Lynch syndrome	MLH1, MSH2, MSH6, PMS2, EPCAM	Autosomal dominant	1:440	5-10	3.7%
Cystic fibrosis	CFTR	Autosomal recessive	3:10000	5	<5%
Ataxia telangectasia	ATM	Autosomal recessive	1:40000-100000	3-8	<5%

*Prevalence of BRCA1/2

***Table 5**: Non-genetic risk factors for developing pancreatic cancer.*

Condition	Relative risk	Lifetime risk
Chronic pancreatitis	14	~5%
Type 1 or new onset type 2 diabetes	2-8	<5%
Obesity	2	<5%
Smoking	2	<5%

Of the acquired pancreatic conditions that carry an increased risk of pancreatic cancer, mucinous cystic neoplasm and main- or branch-duct type IPMNs have significant increased lifetime risk of developing pancreatic cancer that warrant interval surveillance (MRI or EUS). Currently, there are a number of guidelines on the management of these high-risk cystic neoplasms and this will not be further discussed in this review. Longstanding chronic pancreatitis is another risk factor for developing pancreatic cancer where screening may be justified. Although smoking, obesity and diabetes (type 1 and new onset type 2) are risk factors for pancreatic cancer, the proportion of attributable disease is small and they are not current indications for screening.[49]

EUS and MRI/MRCP 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.[46] The high resolution of EUS enables the detection of lesions 5mm (or smaller), which can also be biopsied for tissue diagnosis during the procedure.[46,50] MRCP is the best modality for visualising cyst communication with the main pancreatic duct.[51] ERCP is not recommended due to risk of pancreatitis and low yield.[46] Ca19-9 has no role in detection of precursor lesions or early pancreatic cancer. Currently many biomarkers are under research (serum carcinoembryonic antigen-related cell adhesion molecules [CEACAM], Span -1, MIC-1, pancreatic juice analysis for Kras mutation), but not currently in routine clinical use.

The age with which to commence screening varies depending on the condition and also remains an evidence-free zone. The CAPS consortium recommends patients with hereditary chronic pancreatitis commence screening at 40 years of age, since there is a younger age of onset of pancreatic cancer. Other subjects with high-risk conditions should commence screening at age 50 years or 10 years younger than the youngest pancreatic cancer in the family. Smoking is a strong risk factor in familial pancreatic cancer kindreds, particularly in men and people less than 50 years old, as it increases the risk of pancreatic cancer by 2-3.7 times over the inherited predisposition and lowers the age of onset by 10 years.[52] Currently, there is no consensus as to when screening should cease and should be judged on an individual basis.

Patient preference and fitness for surgery are important factors, which should be incorporated into the decision-making.

The optimal interval for surveillance also remains unclear. Available data from the CAPS Consortium suggest a 12-month surveillance interval for high risk individuals with no pancreatic lesions found at baseline assessment.[46] For those with abnormalities found on baseline imaging, the interval varies dependent on the nature of the lesion. Non-suspicious cysts should have surveillance after 6-12 months, while newly detected indeterminate solid lesions or indeterminate main pancreatic duct strictures should have repeat imaging at three months. Subjects with IPMN should continue surveillance according to the international consensus guidelines.[53]

Current data supporting screening is limited to prospective observational studies in high-risk individuals (table 6).[22,50,51,54-60] Poley et al were the first to evaluate the role of EUS, MRI and/or CT scans in screening of 44 high risk individuals, consisting those with a history of FCP, PJS, familial atypical multiple mole melanoma syndrome (FAMM) and BRCA2.[55] Seven patients had branch duct IPMNs and three had pancreatic adenocarcinoma, proven on surgical resection. The largest study to date (n=192) is a multicentre, prospective cohort study (CAPS 3) of high-risk individuals, using CT, MRI and EUS imaging.[51] Positive findings were detected in 42% (92/216) of patients. Pancreatic mass (84 cystic and three solid) and dilated pancreatic duct (n=5) were identified by one of the imaging modalities and prevalence of these lesions appeared to increase with age. Of all imaging modalities, EUS appeared to have the highest diagnostic yield (CT, MRI and EUS detected pancreatic abnormality in 11%, 33.3% and 42.6% of patients respectively). Among the pancreatic lesions, 82 were IPMNs and three pancreatic neuroendocrine tumours. Five patients underwent surgery and three of them had high grade dysplasia in <3cm IPMNs and multiple intraepithelial neoplasms, suggesting that screening of asymptomatic high risk individuals can detect curable non-invasive high grade lesions. In contrast, the National German Familial Pancreatic Cancer Registry reported a lower rate of pancreatic abnormalities in their high risk individuals (5%), with the majority of the abnormalities being non-malignant.[22,56] This study was the first to raise concern about the potential harm of a screening program and highlights the extreme importance of discussing all positive findings in a pancreatico-biliary multi-disciplinary meeting to determine the optimal surveillance interval, need for biopsy, further investigation or surgery.

Overall, the current data indicate that diagnostic yield of neoplastic pancreatic lesions varies significantly (5% to 50%), whereas the detection rate for pancreatic cancer is only 1% to 2% (table 6). These data are consistent with the findings from a recent systematic review of 542 high-risk individuals screened.[61] The vast range seen in those studies is likely due to differences in the definition of high-risk subjects, measured outcomes and use of varying screening modalities. In particular, the definition of 'positive yield' varies from precursor lesion (cysts, branch duct IPMN) to early cancer. As such, most recent studies that defined positive yield as early stage 1 cancer or high-grade dysplastic precursor lesions often have a lower detection rate (1-2%), whereas those that included cystic lesions, IPMNs or PanINs of any grade of dysplasia tend to report a much higher yield (up to 50%).[50,54,58,60]

The ability to detect 'PanIN' lesions by EUS is controversial and the sonographic features of PanIN are non-specific and not well validated. PanIN may have sonographic features similar to that of chronic pancreatitis, as PanINs are multifocal and are often associated with lobular centric atrophy and fibrosis,[62] which are also seen in chronic pancreatitis or age related parenchymal fibrosis.[46] Furthermore, the ability to recognise 'lobularity' on EUS is very operator-dependent, and cannot be distinguished from other disease processes.

***Table 6**: Summary of studies on screening and surveillance of pancreatic cancer in high-risk individuals.*

Study (reference)	Screening modality	Sample size	At-risk population	All lesions identified (%)	pancreatic cancer identified (%)
Canto et al. 2004	EUS	38	5	5 (13%)	1
Canto et al. 2006	EUS	78	6	6 (8%)	1
Poley et al. 2009	EUS	44	FPC, PJS, BRCA, p16, p53, HP	7 (16%)	3
Langer et al. 2009	EUS, MRCP	76	FPC, BRCA	4 (5%)	0
Verna et al. 2010	EUS, MRCP	51	FPC, BRCA, p16	4 (8%)	2
Ludwig et al. 2011	MRCP	109	FPC, BRCA	7 (6%)	1
Al-Sukhni et al. 2012	MRCP	262	FPC, PJS, BRCA, p16, HP	19 (7%)	2
Schneider et al. 2011	EUS, MRCP	72	FPC, BRCA, PALB2	11 (15%)	1
Vasen et al. 2011	MRCP	79	P16	14 (18%)	7
Canto et al. 2012	MRCP, EUS, CT	216	FPC, BRCA, PJS	93 (43%)	1

Several studies have addressed the psychological impact of screening programs. Axilbund et al found genetic counselling to be helpful to more than 90% of high-risk individuals despite the inability to identify a causative gene.[63] More importantly, patients who participated in a screening program did not experience increased anxiety or perception of cancer risk,[64] and 80% of the participants felt the advantages of screening outweighed the risks.[65] Overall, available data suggest that screening is not associated with any adverse impact on the patient's psychology.

Conclusion

Pancreatic cancer carries a dismal prognosis, largely due to the late stage of disease at presentation. Early detection is of utmost importance given that surgical resection is the only treatment option that is curative at least in some cases. There are multiple suitable imaging modalities (EUS, MRI/MRCP and MDCT) used for detection and staging of pancreatic cancer, each with its own strengths and weaknesses. EUS FNA is the preferred method for tissue diagnosis of pancreatic masses and may be used in conjunction with pancreas protocol CT for staging. Screening for pancreatic cancer in high-risk individuals is currently driven by consensus guidelines recommended by the International CAPS consortium. Long-term outcome data to determine the clinical impact and utility of a screening program, especially on survival, are awaiting. It is therefore important that all screening programs are conducted in a research setting within centres with the appropriate training and expertise in performing EUS in high-risk individuals.

Conflicts of interest

Dr Phan has no conflicts of interest.

Dr Saxena has received consulting fees from Olympus Australia, Pentax Medical and Cook Medical. She is a consultant for Boston Scientific. She has received research support from Cook Medical and Boston Scientific. She is on the scientific advisory board member for Oncosil Medical Ltd.

Dr Alina Stoita has no conflicts of interest.

A/Prof Nguyen has no conflicts of interest.

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