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Pancreatic Cancer Screening: Attempts and Possibilities

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Abstract

Pancreatic cancer has one of the highest disease specific mortality of any malignancy, despite significant advances in diagnosis and treatment over the past decade. Currently there are no efficient screening tools available that can be recommended outside a high-risk population. Screening of high-risk populations has been suggested for early detection of curable pancreatic cancer to improve outcome. There is still however, a lack of an ideal screening method. Efficient and reliable screening methods to achieve early detection of pancreatic cancer are therefore required.

Abbreviations: CT: Computed Tomography; EUS: Endoscopic Ultrsonography; FAMMM: Familial typical Multiple Mole Melanoma syndrome; FPC: Familial Pancreatic Cancer; HBOC: Hereditary Breast Ovarian Cancer; HNPCC: Hereditary Non-Polyposis Associated Colorectal Cancer; HP: Hereditary Pancreatitis; IPMN: Intraductal Papillary Mucinous Neoplasia; MRCP: Magnetic Resonance Cholangiopancreatography; PCMS: Pancreatic Carcinoma Melanoma Syndrome; PJS: Peutz Jeghers Syndrome

Introduction

Mortality rates for pancreatic cancer in developed nations steadily increased from 1950 to 1980. It is predicted that by 2030 pancreatic cancer will be the second leading cause of cancer mortality in the US [1]. In Europe, pancreatic cancer is the 7th most common cancer and accounts for around 138,100 global deaths a year in men and 127,900 deaths a year in women [2]. Baltic countries, and some central/eastern and northern European countries exhibit the highest incidence of pancreatic cancer in the world with rates of over 9.5 per 100 000 in men and 6 per 100 000 in women. Japan, the USA, Russia and the rest of Europe have similar incidence rates of around 7 to 9 per 100 000 men and 5 to 6 per 100 000 in women [3]. Pancreatic cancer carries a very bad prognosis despite advances in diagnosis and management; with an overall 1-year survival rate up to 28.3% [4]. From 2004 to 2010 the 5 year survival of patients diagnosed with pancreatic cancer in the US was 7%. This is a statistically significant improvement when compared to the seventies when the 5 year survival was as little as 3% however pancreatic mortality rates are markedly worse than most other malignancies [5].

There are numerous factors why pancreatic cancer is synonymous with a terrible prognosis but the absence of clinical symptoms often leads to late presentation. Patients often have metastatic or unresectable disease at the time of primary presentation. Like all malignancies it is hoped that if a viable screening tool is available it may be possible to identify the precursor to invasive malignancy or early invasive malignancy. In turn interventions can be put in place to potentially improve survival. Currently screening for pancreatic cancer is limited to a very select population with a high risk of developing pancreatic malignancy.

High risk individuals include those with hereditary pancreatitis who have a cumulative risk of 40% of developing pancreatic cancer which may increase further to 75% with a paternal inheritance pattern [6]. Hereditary pancreatitis is due to a defect in chromosome 7q35 that causes a mutation in trypsinogen which in turn predisposes patients to pancreatitis and pancreatic cancer. Peutz Jegher syndrome is associated with an 11% risk of pancreatic cancer at the age of 70 [7]. Hereditary breast and ovarian cancer syndromes, familial melanoma, and Lynch syndrome are all associated with an increased risk of pancreatic cancer [8]. Screening at present for high risk populations includes a combination of both endoscopic ultrasound.

(EUS) and magnetic resonance imaging (MRI) which are both expensive and invasive and therefore not appropriate for lower risk populations [9,10].

Ductal adenocarcinoma of the pancreas encompasses 80% of all pancreatic malignancies and therefore most malignancies are exocrine in origin. 5% to10% of patients have an underlying germ line disorder, while the remaining cases are thought to be caused by somatic mutations. Some individual studies suggest that mutations in various polymorphic genes can lead to small increases in the risk of pancreatic cancer, but these findings need to be replicated [11]. Mutation of KRAS is detected in more than 80% of pancreatic cancer. KRAS mutations are mostly a G12V or G12D mutation of which more than 80% exhibit deletions, mutations or epigenetic alterations principally the *CDKN2* gene. Up to 50% of pancreatic cancers have mutations in the tumour suppressor gene *p53* and 50% will also exhibit mutations or homozygous deletions in the *DPC4/Smad4* gene [4].

Environmental factors play an integral role in determining pancreatic cancer risk. Smoking, obesity, processed meat consumption and excess alcohol consumption have all been exposed as risk factors for pancreatic cancer [12,13]. Increasing age and the male gender are also associated with an increased risk of malignancy. Here we aim to review the literature and guidelines in the different academic societies to identify the subset of population who could benefit from a screening program. We shall analyse screening techniques for pancreatic cancer and outline the best protocol for pancreatic cancer screening.

Diagnosis of Pancreatic Cancer

Histological biopsy of pancreatic cancer is not routine in all cases. Confirmation on imaging by a radiologist with expertise in pancreatic cancer is often sufficient to determine diagnosis and resectability. Histology is indicated in unresectable tumours or if neoadjuvant treatment is planned and in ambiguous pancreatic lesions in resectable cases. EUS-guided biopsy is the ideal tool to yield tumor tissue as it carries minimal risk of tumour seeding [14]. Percutaneous access e.g. ultrasound or Computed Tomography (CT) guided biopsy are commonly used to biopsy metastatic pancreatic cancer.

Pancreatic Cancer Screening

High-risk populations need pancreatic cancer screening

It is difficult to justify the need to screen all those with an increased risk of pancreatic cancer as the benefits of screening in order to reduce mortality have not been determined. It remains a concern that screening for pancreatic cancer could do more harm than any potential benefit. Many clinical risk factors associated with pancreatic cancer have been identified as age, obesity, smoking, diabetes, and chronic pancreatitis; however, the specificity of these factors to pancreatic cancer is low [15].

Most of pancreatic cancer patients are from populations without significant risk factors. Lack of early symptoms of pancreatic cancer makes early diagnosis of the disease unlikely. Pancreatic cancer usually compresses the bile duct and patients present with painless jaundice. Abdominal pain, back pain or weight loss are usually signs of late-stage disease. Sometimes patients also present with newly diagnosed diabetes or pancreatitis [4].

Screening is suggested in high risk populations for pancreatic cancer, including individuals with lifetime risk over 5% and/or increased relative risk over 5 times proposed by International cancer of the pancreas screening (CAPS) [16]. Proposed high risk populations for pancreatic cancer and their lifetime risk of pancreatic cancer are listed in (Table 1) [15].

Surveillance of high risk groups such as *CDNK2A* mutation carriers is relatively successful, and leads to detection of most pancreatic malignancies at a resectable stage. The benefit of surveillance in families with familial pancreatic cancer is less evident. High-risk populations for the development of pancreatic cancer could be identified at both the local and national level.

Genetic Syndrome	Genes involved	Site of chromosomes	Relative risk (RR) of pancreatic cancer
Hereditary breast/ Ovarian cancer	*BRCA2*	13q12	3.51 fold
	BRCA1	17q21	2.26 fold
FAMM melanoma syndrome	*CDKN2A*	gp21	13-22 fold
Peutz-Jeghers syndrome	*STK11*	19p13.3	132 fold
Lynch syndrome	Mismatch repair genes (*MLH1,MSH2*)	2p22, 3p21	increased
Hereditary pancreatitis	*PRESS1, SPINK1*	7q35, 5q31	50 fold
Cystic fibrosis (heterozygotes)	*CFTR*	7q35	3.5 fold
Ataxia telangiectasia	*ATM*		increased
Fanconi anaemia	*FANCC*	gq22	increased
Familial pancreatic cancer	Unknown	Unknown	Suspected autosomal dominant inheritance
Familial pancreatic cancer	*PALB2*	16p12	High penetrance
Pancreatic cancer in ≥ three first degree relatives			RR=32
Pancreatic cancer in two first degree relatives			RR=6.4
Pancreatic cancer in one first degree relative			RR=4.5

Table 1: Genetic syndromes associated with increased risk for cancer pancreas.

At each centre, genetic disorders and hereditary cancer syndromes could be identified by following pancreatic cancer histories of affected population and their relatives (Table 2) [17], which would enable their risk assessment for disease [18]. This could include genetic testing and DNA analysis.

Study	Screening tools	Cases (n)	Screened population	Diagnostic yield (%)
Brentnall et al. [42]	EUS+ERCP+CT	14	FBC	50
Rulyak et al. [43]	EUS	35	FPC	34
Kimmey et al. [44]	EUS; ERCP*	46	FPC	26
Canto et al. [45]	EUS	38	FPC, PJS	76
Canto et al. [46]	EUS	78	FPC, PJS	22
Poley et al. [47]	EUS	44	FPC, FAMMM, PJS	23
Langer et al. [48]	EUS+MRCP	76	FPC, PCMS	36
Verna et al. [9]	EUS and/or MRCP	51	FPC, FAMMM, HNPCC	EUS: 65
Ludwig et al. [33]	MRCP	109	FPC	MRCP:33 8.3
Vasen et al. [49]	MRCP	79	FAMMM	20
Schneider et al. [50]	EUS+MRCP	72	FPC, BRCA	15
Canto et al. [32]	MRCP, EUS, CT	216	FPC, HBOC, PJS	42.6
Al-Sukhni et al. [31]	MRCP	262	FPC, FAMMM, PJS, HP	32
*Test performed only as an additional test for detected abnormalities				

Table 2: Diagnostic yield, number of population, and techniques of reported pancreatic cancer screening programs.

Successful screening

International cancer of the pancreas screening (CAPS) has proposed a definition of *"successful screening"*, which is the detection and treatment of T1N0M0 margin negative pancreatic cancer and high grade dysplasia, including intraepithelial pancreatic neoplasia-3 (PanIN-3), intraductal papillary mucinous neoplasm (IPMN) with high grade dysplasia, and mucinous cystic neoplasm with high grade dysplasia [15]. Pancreatic cancer has been identified to be a rapidly progressing pathology. Yu et al. [19] showed that of 13,131 patients diagnosed with pancreatic cancer, the mean age of those with stage 4, disease was 1.3 years greater than those with stage 1 disease, suggesting that there is only a limited period of time to potentially screen and identify patients with curative disease. Pancreatic cancer is metastatic at presentation in around 60% of cases and this is believed to be due to rapid disease progression and vague and often absent symptoms [20].

Some authors consider successful screening to be when the benefits outweigh the overall cost of screening. Identification of early stage disease that in turn is resectable has been shown to have an improved prognosis. Overall 5-year survival after resection of large pancreatic cancers (median size 30 mm) is only 10% to 20%, it is 30% to 60% after resection of small tumors (size $\leq$ 20 mm) and exceeds 75% when minute tumours ($\leq$ 10 mm) are resected [21-23]. In turn this mandates large randomized trials to compare the outcomes of people who are subjected to surveillance with an appropriate control subset of the population [16]. Unfortunately, due to the rarity of familial pancreatic cancer undertaking such trials is challenging in contrast to the role of colonoscopy in colonic cancer screening.

The risk factor of pancreatic cancer among the general population is approximately 1 in 10,000 individuals or 0.01%; and with this incidence a positive predictive value of any screening test would be around 0.5%, which would affect the accuracy of the screening.

Therefore, a screening test is unlikely to emerge in the foreseeable future with available information of pancreatic cancer biology and current technology limitations [24].

Age range of pancreatic cancer screening

Incidence of pancreatic cancer is only 10% in patients with cancer syndromes or familial risk factors, these individuals are currently considered suitable for pancreatic cancer screening [24]. The age at which to start screening for pancreatic cancer in order to have an effective screening program in a high-risk population is still arguable. Pancreatic cancer tends to affect hereditary pancreatitis patients very early, and effective screening should begin at age 40 in *PRSS1* (Cationic trypsinogen gene) mutation carriers, which is associated with hereditary pancreatitis responsible for pancreatic cancer in young age [25].

In other high risk groups, there is no agreement regarding screening age range, but most authors recommend starting screening at age of 50, as the average age of diagnosis of hereditary pancreatic cancer is over 65 [16]. Risk factors for pancreatic cancer are relatively nonspecific, and include age, obesity, diabetes, smoking, and genetic chronic pancreatitis. In a smoking population with a family history of pancreatic cancer, we recommend screening to start earlier as they have greater risk than non-smokers [26]; despite there is being no consensus recommendation.

Screening tools

Currently, there is no ideal single screening tool that can be used effectively to identify pancreatic cancer. Reported diagnostic yields of the various screening modalities have ranged between 1.3% to 50% [16]. There is no specific tumor marker for pancreatic cancer, and CA19-9 is of limited diagnostic value as it is not specific for pancreatic

cancer. In addition, some patients are not able to synthesize it, such as people lacking the Lewis antigen. It is normally found in jaundiced patients, and so it might be best used as an indicator for recurrence [4].

Despite this serum level of CA19-9 is the most commonly used serum marker in pancreatic cancer screening; however, the sensitivity and specificity are very limited [27]. A feasibility study attempting to identify pancreatic cancer using an elevated CA19-9 and the referral for EUS showed that in 546 patients with a single first degree relative with pancreatic cancer, only 1 pancreatic adenocarcinoma was found at a cost of more than $40,000 [10]. CA 19-9 in combination with newer screening modalities such as microRNA biomarkers in whole blood and serum metabolism profiling has shown improved sensitivity however their role in clinical practice has not yet been clarified [28,29].

Imaging plays a key role in the diagnosis and staging of cancer however there is at present no suitable imaging technique to screen the population as a whole for pancreatic cancer. Initial diagnosis of intra-abdominal conditions is often facilitated by trans-abdominal ultrasound. It is noninvasive, avoids radiation and is readily available in most healthcare institutes. Imaging of the pancreas using trans-abdominal ultrasound is fraught with problems. The presence of gas within the stomach, small bowel or colon reduces the sensitivity of identifying a pancreatic neoplasm and therefore is not suitable for the diagnosis of small pancreatic neoplasia.

The most commonly used screening tools for pancreatic cancer are endoscopic ultrasonography, computed tomography and magnetic resonance imaging with magnetic resonance cholangiopancreatography (MRCP). MRI with MRCP and EUS are considered the most accurate tools for pancreatic imaging used for the screening purposes [30-33]. MRI with MRCP is a non-invasive procedure with high accuracy in detection of very minor changes in pancreatic parenchyma and pancreatic ducts. EUS is very sensitive for lesions less than 1 cm, however, it is invasive and operator dependent [15]. CT, in addition to radiation exposure, has very low sensitivity in the detection of pancreatic dysplasia and is suboptimal as a screening tool. ERCP has a low diagnostic sensitivity and has a risk of pancreatitis, and therefore they are not recommended for screening [16,24]. Some biomarkers of cells obtained from pancreatic ductal brushing and cytology have been identified. However, they offered little screening sensitivity over serum biomarkers to diagnose pancreatic cancer [34]. The role of positron emission tomography scanning (PET) is still unclear in pancreatic cancer. Chronic pancreatitis is very difficult to differentiate from pancreatic cancer and in turn it has a low specificity for detecting pancreatic cancer [35].

The prospective CAPS3 study [32] performed comparisons of EUS, secretin-enhanced MRI/MRCP and pancreatic-protocol CT for one-time screening; identification of pancreatic lesions was 42.6%, 33.3% and 11% of a screened high-risk population respectively. The study reported that EUS and MRI are better than CT for the detection of small, predominantly cystic pancreatic lesions and MRCP provided the best tool to identify communications between the cystic lesion and the main pancreatic duct. Further studies continue to support the use of EUS and MRI as complementary modalities rather than interchangeable tools. EUS and/or MRI have been shown to detect pancreatic cancer in 6% of high risk individuals [36].

Newer screening methods have been investigated with promising results but still need more evidence to be used in the clinical setting. Circulating cell free DNA is also being investigated as a possible biomarker for screening, and one study successfully used methylation patterns in cell-free plasma DNA in differential detection of pancreatic cancer [37]. Glypican-1 circulating exosomes (GPC1 crExos) have also been identified as a possible mechanism to identify early pancreatic cancer. GPC1 crExos were detected in the serum of patients with pancreatic cancer with absolute specificity and sensitivity, distinguishing healthy subjects and patients with a benign pancreatic disease from patients with early- and late-stage pancreatic cancer [38].

Surveillance for screened individuals without pancreatic lesions

There is no agreed recommendation about the age to exit screening pathways for those patients, as the vast majority of individuals who developed relevant lesions during follow-up imaging had pancreatic abnormalities at initial screening [39]. Patients who developed advanced pancreatic cancer after normal/indeterminate initial imaging were diagnosed beyond 12 months; therefore 12 months interval from the baseline is suggested [40]. In the available published studies, the same imaging tests for baseline imaging have been used for the follow-up [16].

Follow-up after surgical treatment in High-risk population

It is important to bear in mind that there is no clear advantage in an earlier detection of recurrences [4]; therefore a follow-up schedule should be discussed with patients to avoid emotional stress and economic burden. In the case of an elevated preoperative serum CA19-9, follow-up with this marker could be performed every 3 months for 2 years and an abdominal CT scan every 6 months. Another strategy could be simply to base follow-up imaging on symptoms.

International Consensuses, Guidelines and Recommendations for Pancreatic Cancer Screening

Summary of International Cancer of the Pancreas Screening (CAPS) consortium 2011

An international CAPS consortium summit with 49 multidisciplinary experts was held in 2011 to develop consensus guidelines for pancreatic cancer screening [16]. The group recommends:

- Screening with EUS and /or MRI/MCRCP for high-risk individuals.
- High risk population include: first degree relatives of patients with pancreatic cancer from familial kindred's, carriers of p16 or BRCA2 mutations with an affected first-degree relative; patients with Peutz-Jeghers syndrome; and patients with Lynch syndrome and an affected first degree relative with pancreatic cancer.
- The optimal management of patients with detected pancreatic lesions, the age to begin screening and screening intervals need to be properly outlined.

Summary of European Society for Medical Oncology (ESMO) guidelines and recommendations 2012

Screening of pancreatic cancer: EUS and MRI are recommended only to screen high-risk population.

Diagnosis of pancreatic cancer: EUS, contrast-enhanced MDCT and MRI combined with MRCP are most appropriate for diagnosis; while

the role of ERCP is limited to relieve biliary obstruction by stenting if surgery cannot be done promptly. Baseline CA19-9, in absence of cholestasis, may have a prognostic value. Tissue biopsy is not mandatory before surgery with radical intent; however, in some situations were imaging results are ambiguous, EUS guided biopsy is preferred and percutaneous route should be avoided. Tissue diagnosis from locally advanced primary or metastatic lesions can also be obtained percutaneously under ultrasound or CT guidance before palliative therapy.

Summary of National Comprehensive Cancer Network (NCCN) guidelines 2014

- Decisions about diagnosis and management should involve multidisciplinary consultation at a high volume centers [41].
- Specialized CT should be performed according to defined pancreatic protocol such as triphasic cross sectional imaging and thin cuts (3 mm or less). Multiplanar reconstruction is preferred to show relation of tumor to the vessels. MRI pancreatic protocol is emerging. PET/CT scan may be considered to detect extra pancreatic metastases [42-48].
- Biopsy proof of cancer is not required before surgical resection, especially when the clinical suspicion is high. EUS-FNA is the preferable approach in resectable disease because of better diagnostic yield and lower risk of peritoneal seeding compared to percutaneous approach [49,50].
- Staging laparoscopy can be used in patients with high risk of metastatic disease such as patients with borderline resectable disease, markedly elevated CA19-9, large primary tumors of body and tail or large regional lymph nodes. Positive cytology from washings obtained at laparoscopy is equivalent to M1 disease.

Conclusion

In conclusion, pancreatic cancer is an uncommon malignancy with a very poor prognosis. Due to a lack of obvious symptomatology patients present late with unresectable disease. In order to improve survival in a cancer with an exceptionally poor 5 year survival screening has been muted as a potential strategy to reverse this failure in modern healthcare. Identifying the at risk population, encompassing genetic screening, using appropriate imaging modalities particularly EUS as well as providing recommendations to treat and avoid environmental risk factors are important strategies to proactively diagnose and treat pancreatic cancer.

The ideal screening test is yet to be identified with current strategies either having poor sensitivity and specificity or being invasive or having potentially toxicity associated with their application. Screening is currently confined to a high-risk population and is therefore targeted. The problem remains that a population based screening tool remains a long way off. Identification of specific and sensitive biomarkers in blood or pancreatic secretions for pancreatic cancer would be the cornerstone for pancreatic cancer screening in the future especially for an average risk population. With increased global financing for cancer research potentially this will occur in the not too distant future.

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