

Endoscopic ultrasonography for surveillance of individuals at high risk for pancreatic cancer

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Abstract

Pancreatic cancer is a highly lethal disease with a genetic susceptibility and familial aggregation found in 3%-16% of patients. Early diagnosis remains the only hope for curative treatment and improvement of prognosis. This can be reached by the implementation of an intensive screening program, actually recommended for individuals at high-risk for pancreatic cancer development. The aim of this strategy is to identify pre-malignant precursors or asymptomatic pancreatic cancer lesions, curable by surgery. Endoscopic ultrasound (EUS) with or without fine needle aspiration (FNA) seems to be the most promising technique for early detection of pancreatic cancer. It has been described as a highly sensitive and accurate tool, especially for small and cystic lesions. Pancreatic intraepithelial neoplasia, a precursor lesion which is highly represented in high-risk individuals, seems to have characteristics chronic pancreatitis-like changes well detected by EUS. Many screening protocols have demonstrated high diagnostic yields for pancreatic pre-malignant lesions, allowing prophylactic pancreatectomies. However, it shows a high interobserver variety even among experienced endosonographers and a low sensitivity in case of chronic pancreatitis. Some new techniques such as contrast-en-

hanced harmonic EUS, computer-aided diagnostic techniques, confocal laser endomicroscopy miniprobe and the detection of DNA abnormalities or protein markers by FNA, promise improvement of the diagnostic yield of EUS. As the resolution of imaging improves and as our knowledge of precursor lesions grows, we believe that EUS could become the most suitable method to detect curable pancreatic neoplasms in correctly identified asymptomatic at-risk patients.

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Key words: Endoscopic ultrasonography; Pancreatic cancer; Surveillance

Core tip: In the era of early diagnosis and screening programs, endoscopic ultrasound (EUS) represents the most promising tool able to identify pancreatic precursor neoplasms in high risk individuals. If compared to other imaging techniques, it is highly accurate to diagnose small pancreatic cancer and pre-malignant lesions, with very low rate of complications and limitations. Here are reported the current role of EUS in various international screening programs and its future possible developments.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related death in the western world^[1,2], with a median age at diagnosis of 71 years and 45220 new cases and 38460 deaths in 2013 in the United

States^[3]. In contrast to other causes of cancer death (lung, colorectal, breast and prostate), which have declined in the last years, the death rate from PDAC has increased during the same time period^[4]. It is a highly aggressive tumor characterized by an incidence rate almost equaling the mortality rate and an overall 5-year survival of approximately 5%-6%^[1,2]. This dismal prognosis is mainly due to the fact that the tumor is characterized by a locally advanced or metastatic stage at the presentation, low resection rates and poor response to radiotherapy and chemotherapy.

Even though complete resection improves median survival, at the time of diagnosis only 10% to 25% of pancreatic cancer patients will be amenable to potentially curative resection^[5]. Also in this case 5-year survival remains low (10% to 24%)^[6,7].

However, longer survival has been reported for complete resection of early stage tumors thus identifying patients who have early, small, localized tumors at presentation could improve this poor overall survival rate^[8].

Resection of small tumors (< 2 cm or T1) improves 5-years survival (30% to 60%)^[9,10]. However it has been alluded that the better prognosis is for tumors < 1 cm (T1a) with 5-years survival up to 78%^[6,11,12].

To date, however, it might be difficult to detect such a small pancreas cancer, mainly due the fact that more than 90% of PDAC measuring 1 cm or less in diameter are asymptomatic.

Probably the only way to improve survival lies in identifying early disease or precursor lesions through a screening program of asymptomatic individuals.

As premalignant stages of disease have been identified, and the sensitivity of pancreatic imaging has improved with endoscopic ultrasound (EUS) and high-resolution magnetic resonance imaging (MRI), early detection of small curable pancreatic cancers and premalignant lesions now seems possible^[13-16].

Unfortunately, due to the overall low incidence of the disease, accounting for 3% of all new cancer cases in the United States and a life-time risk of 1.3% in the general population, and the lack of simple, safe, accurate, inexpensive, and non-invasive diagnostic tests for early lesions, a widespread screening program does not seem feasible at present.

Multiple risk factors for pancreatic cancer development have been identified like male gender, obesity, African-American or Ashkenazi Jewish descent, nickel exposure, smoking, lack of physical activity, and calorie intake^[17-20].

Beside them, also members of a family with a strong history of disease or individuals with inherited pancreatic cancer syndromes, carrying a known genetic mutation, should be considered at high risk of developing pancreatic cancer (high risk individuals, HRIs)^[21-25]. Screening of these high-risk groups seems to be of benefit since genetic susceptibility and familial aggregation are responsible of 3%-16% of pancreatic cancers^[26-28].

These individuals can be divided into two groups: those who belong to families in which pancreatic cancer

affects at least two first-degree relatives without a known genetic mutation (familial pancreatic cancer, FPC) and those with hereditary syndromes or diseases that predispose to the development of pancreatic cancer (Table 1).

FAMILIAL PANCREATIC CANCER

The former represents the largest proportion of hereditary PDAC.

Prospective studies demonstrated an increased risk of pancreatic cancer in healthy first degree relatives (FDRs), related to the number of family members affected. This risk has been estimated to be 2.3 to 4.5-fold greater in individuals with one FDR with pancreatic cancer, 6.4-fold greater in individuals with two FDRs with the disease and 32 to 57-fold greater in individuals with three or more FDRs affected^[29-32].

Similarly to other familial tumors, the median age of presentation in patients with FPC is up to 20 years earlier than in patients with sporadic cancer (49 years *vs* 61 years)^[33-35] with an "anticipation phenomenon" in the affected kindred and a trend to become more severe and appear at an earlier age as the disorder is passed from one generation to the next^[35,36]. Currently, the genetic etiology of most cases of FPC remains undetermined but complex segregation analysis of these patients has led to the discovery of various candidate pancreatic cancer susceptibility genes such as BRCA2 (6%-17% of cases)^[37,38], partner and localizer of BRCA2 (PALB2) (1%-4% of cases)^[39,40] and palladin, even if mutations of the latter have been identified in normal controls as well^[41-43].

Due to the complex nature of pedigrees, a Mendelian risk prediction tool for PDAC, named PancPRO was developed in 2007.

This is a prediction model for FPC that, using full pedigree data and age of family members, estimates the probability that an asymptomatic individual will develop the disease^[44].

INHERITED PANCREATIC CANCER SYNDROMES

Individuals with certain tumor syndromes have a marked increase in risk of developing pancreatic ductal adenocarcinoma.

These syndromes are represented by familial atypical mole-multiple melanoma, Peutz-Jeghers syndrome, hereditary pancreatitis, cystic fibrosis, familial breast-ovarian cancer, hereditary non-polyposis colorectal cancer, familial adenomatous polyposis, Li-Fraumeni syndrome.

Familial atypical mole-multiple melanoma

Familial atypical mole-multiple melanoma (FAMMM) is an autosomal dominant disease associated with mutations within CDKN2A gene (p16 Leiden)^[45,46]. Its inactivation is associated with PDAC that was found 13 to 38-fold more frequent than expected^[46,47], with a cumulative risk

Table 1 Genetic diseases associated with pancreatic cancer risk

Risk condition	Relative risk	Risk by age 70	Gene
Familial pancreatic cancer			<i>PALLD</i>
1 first-degree relative	2.3-4.5	2%	<i>BRCA2</i>
2 first-degree relatives	6.4-18	3%	<i>PALB2</i>
≥ 3 first-degree relatives	32-57	16%	
Familial atypical multiple mole melanoma	13-38	15%-20%	<i>CDKN2A/p16</i>
Peutz-Jeghers Syndrome	132	11%-60%	<i>STK11/LKB1</i>
Hereditary pancreatitis	50-87	30%-75%	<i>PRSS1</i> <i>PRSS2</i> <i>SPINK1</i> <i>CTRC</i>
Cystic fibrosis	5.3	<5%	<i>CFTR</i>
Familial breast ovarian cancer	3.5-10	5%	<i>BRCA2</i>
	2.3-3.6	1%	<i>BRCA1</i>
Hereditary non-polyposis colon cancer	2.3-8.6	3%-4%	<i>MLH1</i> <i>MSH2</i> <i>MSH6</i>
Familial adenomatous polyposis	4.5-5	2%	<i>FAP</i> <i>MUTYH</i>
Li Fraumeni syndrome	Unknown	Unknown	<i>TP53</i>

by age 75 of 15% to 20%^[48,49].

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome (PJS) is an autosomal dominant genetic disease characterized by an increased risk of various neoplasms, including pancreatic cancer^[50,51] and it is often associated with mutations within *STK11* gene, a tumor suppressor gene. Patients with PJS have a 132-fold increased risk^[50] and an 11%-36% cumulative risk of developing PDAC with an early age of onset (average: 40.8 years)^[50,52]. In this kind of patients, it frequently develops through IPMN^[23,53].

Hereditary pancreatitis

Hereditary pancreatitis (HP) is an inherited form of chronic pancreatitis characterized by mutations within *PRSS1*, *PRSS2*, *SPINK1*, *CFTR* and *CTRC* genes^[54,55]. PDAC is often a consequence of this condition^[56,57] inasmuch so resected pancreata from patients with HP frequently demonstrated PanIN-3 lesions (50%)^[58]. Patients with hereditary pancreatitis have a 53 to 87-fold increase risk^[57,59] with an age of onset at 50 years in smokers^[60]. Lifetime risk is 30% to 75% in patients with paternal inheritance^[57,59].

Cystic fibrosis

Cystic fibrosis (CF) is a disorder associated with mutations within *CFTR* gene with an increased risk for PDAC (5.3-fold)^[61], in fact the histological aspect of CF associated lesions is very similar to that of "classical" chronic pancreatitis, characterized by atrophy of acinar tissue, fibrosis, and inflammation^[62,63].

Familial breast-ovarian cancer

Familial breast-ovarian cancer (FBOC) is an autosomal

dominant inherited disease due to mutations within *BRCA1* or *BRCA2* genes.

The risk of PDAC among *BRCA1* mutation carriers is low (2.3-3.6 fold than general population)^[64,65]. Conversely *BRCA2* mutation carriers had a 3.5-10-fold increased risk^[66,67] and a 5% lifetime risk of pancreatic cancer^[67].

Hereditary non-polyposis colorectal cancer

Hereditary non-polyposis colorectal cancer (HNPCC) is an autosomal dominant genetic condition due to the inherited mutations in DNA-mismatch repair genes, such as *MLH1*, *MSH2*, *MSH6*, *PMS2* and *EPCAM*^[68]. The estimated relative risk of pancreatic cancer is 2.3 to 8.6-fold higher with a lifetime risk of pancreatic cancer (3%-4%)^[69,70]. Carriers of *MLH1* mutations have a higher risk than carriers of *MSH2* (5.6 *vs* 2.3)^[71].

Familial adenomatous polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant disease of the colon caused by mutations within the gene *APC*. Among FAP pediatric carriers, pancreatic adenocarcinoma may represent an extracolonic manifestation of FAP^[72]. The relative risk for pancreatic cancer is 4.5 in patients with the syndrome^[73] and the lifetime risk 2%^[74].

Li-Fraumeni syndrome

PDAC seems to be a part of the cancer spectrum of the Li-Fraumeni syndrome (LFS), a disease caused by mutations within *TP53* gene^[63,75]. It has been estimated that about 1.3% of these patients show pancreatic cancer^[63,76].

PRECURSOR LESIONS

The ideal screening method for HRIs should detect small asymptomatic pancreatic cancers and, mainly, benign non-invasive precursor lesions, to allow for curative surgical resection^[77,78]. In fact pancreatic carcinogenesis should be intended as a multistep phenomenon with progressive changes from the normal pancreatic ductal epithelium to infiltrating carcinoma^[79].

The other three well known precursor lesions are: pancreatic intraepithelial neoplasms (PanINs), intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs)^[78-81].

Pancreatic intraepithelial neoplasia

PanINs are usually asymptomatic and are characterized by microscopic papillary or flat, noninvasive epithelial neoplasms that are usually < 5 mm in diameter and confined to the pancreatic ducts^[78,82].

According to the degree of cytological and architectural atypia, PanINs are divided into three grades^[83]: PanIN-1: minimal atypia; flat (PanIN-1A) and papillary types (PanIN-1B); PanIN-2: moderate atypia; PanIN-3: severe atypia.

The evidence that this kind of lesions are linked to invasive carcinoma is based on clinical associations and

genetic analysis^[81,84-86].

Mucinous cystic neoplasms

Mucinous cystic neoplasms (MCNs) are cystic epithelial neoplasms that occur almost in women, lack of communication with the pancreatic ductal system and have a predilection for the body and tail^[80,87].

Malignancy rates of resected MCNs vary from 6% to 36%^[80] and usually resembles common ductal adenocarcinoma.

Intraductal papillary mucinous neoplasms

Intraductal papillary mucinous neoplasms (IPMNs) are a more aggressive neoplasm compared to MCNs. They represent a disorder of the pancreatic ductal system, characterized by cystic dilatation. Clinically, three different varieties exist: main duct type characterized by diffuse dilatation of the main pancreatic duct, branch duct type (IPMN-BD) appearing as dilatation of branch ducts, and mixed-type involving both of them.

These lesions are thought to undergo transformation from adenoma to borderline neoplasms, and finally to carcinoma, similarly as seen with PanINs.

Patients with IPMN-MD have a risk of malignancy of approximately 50%-90%^[16,86-89], *vs* 6%-46% in patients with IPMN-BD^[16,87,89,90]. In these patients, the risk of malignancy increases with presence of symptoms, mural nodules and size over 3 cm^[89]. IPMNs are mainly present in familial pancreatic cancer kindred and in PJS and FAP patients where seems to have a more aggressive biological behavior (increased growth rate and degeneration) compared to sporadic IPMNs^[22,91]. IPMNs are more prevalent in high risk individuals than in the general population (16%-42% *vs* 0.2%)^[92], moreover they are commonest in specimens from FPC than in sporadic PDAC (33% *vs* 6%)^[81].

SCREENING

The goal of screening could be the reduction of pancreatic cancer-related mortality. As previously reported, surrogate end point in pancreatic cancer could be the identification and resection of potentially curable lesions (high-grade precursors and early invasive carcinomas). There is no evidence that diagnosing these lesions will improve survival, but there are data suggesting that resection of very early disease is associated with better prognosis^[93,94]. However, no consensus opinion could be reached on the best suitable approach for screening until available imaging modalities and biomarkers will become adequate to detect early stage cancer. Actually, serum markers, computed tomography, magnetic resonance (MRI) \pm cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography and endoscopic ultrasound haven't all the features of an effective screening tool^[95-100]. Describing the screening modalities is beyond the aim of this review. Whatever the approach a surveillance program should be recommended for patients with a risk of

PDAC development greater than 10-fold^[22,23,77].

This degree of risk includes family members with \geq 3 first-degree relatives with pancreatic cancer and patients with hereditary pancreatitis, FAMMM and PJS.

A screening test should also be performed in individuals with syndromes associated with pancreatic cancer and known high-risk factors, such as cystic neoplasia, duct ectasia, diabetes mellitus, smoking history and chronic pancreatitis^[101]. To evaluate the risk to develop pancreatic cancer can be used mathematical models, such as the PancPRO model (see above).

No clear consensus was achieved on when to start screening. It seems reasonable to start at 40-50 years of age (30 years for PJS) or 10-15 years earlier than the younger kindred affected by pancreatic cancer^[21,22,96,102].

There is no consensus also on the frequency, because evidence on the natural history and rate of progression of pancreatic cancer in high risk patients is still lacking. However, yearly screening seems to be the most suitable approach^[21,22,36,103] even if some centers recommend 3 years intervals in case of negative screening exam and absence of other risk factors associated. A more aggressive protocol can be used for patients with abnormal findings at the last screening^[52]. In these cases a subsequent screening could be done every 3-6 mo^[22,103] or every 3-12 mo^[21,36,100].

The majority of studies have generally used the same imaging test for surveillance as for baseline screening, while others suggest an alternating use of MRI/MRCP and EUS^[36,98] (Figure 1).

ROLE OF ENDOSCOPIC ULTRASONOGRAPHY

Endoscopic ultrasonography (EUS) is known as a powerful imaging tool for studying pancreatic diseases. In particular it has been described as a very accurate imaging technique for early detection of pancreatic cancer providing high-resolution images of the pancreas without the risk of radiation exposure and identifying mural nodules (focal thickening of the wall in branch duct IPMNs), which are associated with increased risk of malignancy^[16,82]. With its high resolution, in experienced hands it is able to detect focal lesions as small as 2-5 mm^[22,104-106] with the possibility of taking bioptic samples by fine needle aspiration (FNA) for histopathological examination. EUS has been described as a highly sensitive method for pancreatic malignancy^[107], but results for accuracy differ. Early studies have shown a better accuracy in detecting PDAC for EUS compared with dual phase helical CT (97% *vs* 73%, respectively)^[108]. This results were also confirmed when EUS was compared with multiphase helical CT (98% *vs* 86%, respectively)^[107,109]. The prospective CAPS3 study is the first blinded study that compared standardized pancreatic protocol CT, secretin-enhanced MRI/MRCP and EUS for one-time screening in HRIs. It showed that EUS and MRI are better than CT for the detection of small, cystic, pancreatic tumors, with a diag-

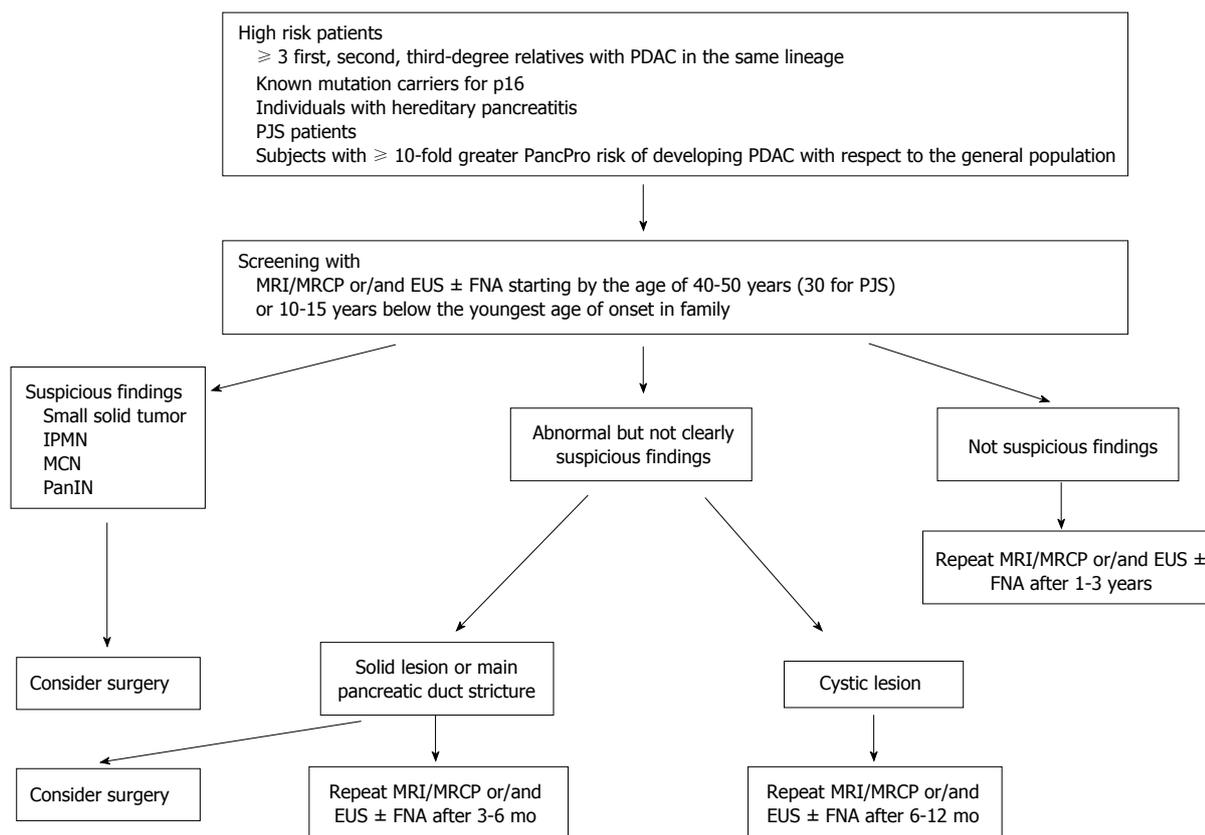


Figure 1 Management algorithm for individuals at risk of pancreatic cancer. EUS: Endoscopic ultrasonography; ERCP: Endoscopic retrograde cholangiopancreatography; CT: Computed tomography; FNA: Fine needle aspiration; PDAC: Pancreatic ductal adenocarcinoma; PJS: Peutz-Jeghers syndrome; MRI: magnetic resonance imaging; MRCP: Magnetic resonance cholangiopancreatography; IPMN: Intraductal pancreatic mucinous neoplasia; MCN: Mucinous cystic neoplasm; PanIN: Pancreatic intraepithelial neoplasia.

nostic yield of 42.6%, 33.3% and 11%, respectively^[110]. EUS was also found to be superior to MRI and CT in sensitivity regarding the detection of IPMN-derived and -concomitant PDACs at the first examination (100% *vs* 53% and 53% and 61% *vs* 33% and 39%, respectively) and during a 5 years follow-up period (100% *vs* 50% and 56%, respectively)^[111]. In this setting EUS detected PDACs significantly better than the other modalities and it appears to be more useful than CT and MRI for the early detection of pancreatic cancer (Table 2).

Another recent study^[112] has shown an incremental increase in diagnostic yield of EUS-FNA over CT (36%) and MRI (54%) for prediction of a neoplastic cyst and an increase in overall accuracy for diagnosis of neoplastic pancreatic cysts by the addition of EUS±FNA.

A normal EUS examination seems to have a high negative predictive value (NPV)^[113]. Two recent studies including patients with suspicion of pancreatic cancer followed for 23.9 and 25 mo, respectively, showed that none of those with a normal EUS evaluation developed pancreatic cancer (NPV = 100%)^[114,115].

Furthermore, EUS-guided fine needle aspiration (EUS-FNA) may provide a histological diagnosis of cancer and a means of detecting dysplasia in precancerous lesions^[23]. A recent meta-analysis has demonstrated that EUS-FNA is highly sensitive (89%), specific (96%), accurate (97%) and has a very good positive likelihood

ratio (16.08) and an acceptable negative likelihood ratio (0.13)^[116]. Moreover, another recent study not included in the meta-analysis previously reported^[117], confirmed these values and has shown that the diagnostic accuracy of EUS-FNA could be further improved by the addition of pancreatic juice analysis.

EUS complications are rare and the risk of perforation is similar to standard upper endoscopy (< 0.03%). Also EUS-FNA of pancreatic lesions can be considered a safe technique, especially if several technical points are taken into account in each specific situation the endosonographer perform a FNA^[118]. The two major complications after a FNA are pancreatitis (0%-2%)^[119,120] and bleeding (0% to 1.3%)^[121,122], while the risk of infection exists only when mucinous cystic lesions are involved^[118]. No deaths were reported^[120-123].

Actually, the diagnosis of PanINs by imaging tests is very challenging. The surgical resection of early curable neoplasms detected during screening programs in at-risk individuals has permitted to study the morphology of unadulterated precursor lesions in this kind of patients^[21,81]. In particular: (1) PanINs are frequently associated with lobulocentric atrophy and fibrosis; and (2) PanINs are often multifocal.

The combination of these alterations produces grossly appreciable changes in the pancreas with a mosaic of fibrosis, atrophy and uninvolved parenchyma, very similar

Table 2 Endoscopic ultrasound-based studies on screening for individuals at risk for pancreatic cancer

Ref.	No. of patients	High-risk groups	Imaging test	Target lesions	Diagnostic yield	Limits of the study
Brentnall <i>et al</i> ^[21]	14	FPC	EUS + ERCP + CT	PanIN \geq 2	50%	
Kimney <i>et al</i> ^[104]	46	FPC	EUS	PanIN \geq 2	26%	
Canto <i>et al</i> ^[22]	38	FPC, PJS	EUS	IPMN, PC	5.30%	Low PPV
Canto <i>et al</i> ^[23]	78	FPC, PJS	EUS	IPMN, PC, PanIN \geq 2	10.20%	
Poley <i>et al</i> ^[35]	44	FPC, PJS, FAMMM	EUS	IPMN, PC	22.70%	No pathological confirmation of IPMN
Langer <i>et al</i> ^[105]	76	FPC, FAMMM	EUS + MRCP	IPMN	1.30%	Moderate risk patients
Verna <i>et al</i> ^[62]	51	FPC, FBOC	EUS and/or MRCP	IPMN, PC, PanIN \geq 2	12%	
Schneider <i>et al</i> ^[36]	72	FPC, FAMMM	EUS + MRCP	IPMN	12.50%	No pathological confirmation
Canto <i>et al</i> ^[110]	216	FPC, FBOC, PJS	EUS + CT + MRCP	IPMN, PC	39%	Mainly no pathological confirmation

FPC: Familial pancreatic cancer; PJS: Peutz-Jeghers syndrome; FAMMM: Familial atypical multiple mole melanoma; FBOC: Familial breast ovarian cancer; EUS: Endoscopic ultrasonography; ERCP: Endoscopic retrograde cholangiopancreatography; CT: Computed tomography; MRCP: Magnetic resonance chol angiopancreatography; PanIN: Pancreatic intraepithelial neoplasia; IPMN: Intraductal pancreatic mucinous neoplasia; PC: Pancreatic cancer; PPV: Positive predictive value.

to chronic pancreatitis^[81,124].

These quite subtle ductal and parenchymal changes are often detectable by EUS using standard criteria for the diagnosis of chronic pancreatitis, such as heterogeneity, multifocal lobularity, echogenic foci, hypoechoic nodules, strands and dilated main and branch pancreatic ducts^[22,124,125].

In literature, chronic pancreatitis-like changes are found in variable rates. The John Hopkins group detected these findings in 45% and 61% of the examined HRIs in whom they were significantly more common, compared with control subjects, regardless of age and alcohol exposure^[22,23]. This ultrasonographic diagnosis of chronic pancreatitis was surgically confirmed in all but one of the HRIs who underwent surgery. Furthermore, all but 1 of these patients had branch duct-type IPMNs^[22]. In the University of Washington study, the authors suggested that the pancreatitis-like changes, which are part of the phenotype of FPC kindreds, are expression of an underlying pancreatic dysplasia rather than chronic pancreatitis^[21]. Finally the German group reported a relative low prevalence (22.4%) with all but one normal findings at MRI/MRCP evaluation^[103].

These studies suggest that features of chronic pancreatitis should be noted during screening because although the precursor lesions may be too small to visualize by currently available imaging technologies, the effects they produce such as cysts and nodules in a background of intact parenchyma, can be detected by EUS in the hands of an experienced operator.

This was also confirmed in IPMNs. In a recent study conducted on forty patients, who underwent resection for IPMN, PanIN was researched on surgical specimens and the pathological data were compared with endosonography features. EUS changes corresponded to PanIN lesions in 83% of cases and it was able to detect 69% of patients with PanIN lesions (57% of those with panIN-3)^[126].

Nevertheless, the presence of a chronic pancreatitis drastically reduces the diagnostic value of EUS, because of the intraductal and parenchymal changes associated

with chronic inflammation and fibrosis could not be differentiated from premalignant pancreatic lesions^[127].

In summary the clinical significance of these changes in HRIs remains unclear. They may be indicative of a precursor lesion of PDAC, but these data must be carefully assessed.

Another field of application for EUS in HRIs is in differentiation between focal pancreatitis and pancreatic cancer. Contrast enhanced EUS seems to be a promising technique due to perfusion characteristics of microvessels^[128]. Hocke *et al*^[129] analyzed the sensitivity and specificity for the diagnosis of pancreatic carcinoma of conventional endoscopic B-mode, power Doppler ultrasound and contrast-enhanced power mode. They reported an increase from 73.2% to 91.1% and from 83.3% to 93.3% respectively, with the use of contrast-enhanced power mode *vs* conventional EUS. The major limits of EUS are: (1) high interobserver variety, even among experienced endosonographers, especially for diagnosis of pancreatitis like changes^[130,131]; (2) the need for sedation because of the minimally invasive nature of the procedure; (3) the need of additional clinical and imaging information^[112] to improve accuracy as demonstrated by Meining *et al*^[132] who reported a worse overall accuracy for a strictly blinded EUS examinations (61.1%) compared to the accuracy of routine and unblinded evaluation with additional imaging information (72.2% and 75.0%, respectively); (4) Low sensitivity in case of chronic pancreatitis, diffusely infiltrating cancer and a recent episode of acute pancreatitis^[133,134]; and (5) Low availability outside major centres.

Currently, many international screening protocols are available throughout the world and the majority of them use EUS as the main imaging tool for screening, because of its ability to detect masses < 1 cm^[21-23,132,135], with CT or MRI/MRCP scans and ERCP proposed in combination with EUS^[136].

The first EUS-based screening program was prospectively conducted by Brentnall *et al*^[21] at the Washington University, on a small group of 14 high-risk patients from three unrelated pancreatic cancer kindred that had two

or more affected members in at least two generations. The study evaluates an EUS- and ERCP-based approach with the aim to detect pancreatic cancer precursor lesions (PanINs). The EUS and ERCP suspected signs of PanINs were no specific chronic pancreatitis-like changes. Seven patients (50%) had an abnormal EUS and ERCP histological confirmed as precancerous changes in the pancreas (PanIN-2 and 3) without any invasive cancer.

A follow up study of the same group confirmed a high yield (26%). It was based on a large cohort of 46 patients and was conducted using EUS as the first diagnostic approach, with ERCP for patients with EUS abnormalities. Twelve patients with imaging abnormalities were referred to histological examination and all of them revealed widespread precancerous lesions (PanIN 2 e 3), without evidence of invasive pancreatic cancer^[136].

Canto *et al*^[23] screened HRIs for early pancreatic neoplasia with an EUS-based and an EUS- and CT-based^[22] prospective controlled study at Johns Hopkins University. In the former approach they used EUS to screen 38 asymptomatic individuals from high risk families (≥ 3 affected relatives and PJS). Six pancreatic lesions were detected: four benign masses and two neoplastic (one adenocarcinoma and one IPMN; screening yield of 5.3%). Either the CT or ERCP evaluations did not detect the single PDAC. In the latter one, pancreatic abnormalities were compared in 78 high-risk individuals (72 from FPC kindred and 6 PJS) and 149 control patients. If the EUS was abnormal, EUS-FNA and ERCP were performed. This approach found 8 patients with pancreatic neoplasms (10.2%) confirmed by surgery or FNA (6 patients had benign IPMNs, 1 had an IPMN with invasive ductal adenocarcinoma and 1 patient had PanIN-3) and no pancreatic neoplasia among the control subjects. All of the lesions visualized by CT were also detected by EUS, while CT missed two IPMNs > 1 cm in the second study and one pancreatic cancer in the first one. Moreover, ERCP correctly diagnosed only 2 of the 7 confirmed IPMNs seen by EUS.

In contrast to these findings, Langer *et al*^[103] published their results of a prospective screening study conducted by the National German Familial Pancreatic Cancer Registry (FaPaCa) on 76 individuals from 34 FPC and FAMM kindreds. The protocol included CA 19-9 and CEA serum values, EUS, and MRI combined with MRCP at the screening visit. EUS-FNA was performed in the case of indefinite abnormalities and in case of diffuse parenchymal irregularities. Only three serous cystadenoma, one IPMN, three PanIN 1 and one PanIN 2 were pathologically confirmed. Three of them, the smaller ones, were detected by EUS, but not by MRI. No cancers were identified and only IPMN was considered a significant precancerous lesion for a diagnostic yield of 1.3%.

This lower yield could be explained by the fact that this study included also a large number of patients at a moderate risk (< 10 -fold) with a fraction of high-risk patients of 42% *vs* 55% for the second study of the Johns Hopkins University. Moreover, PanIN 1 e 2 and serous cystadenoma were not considered precancerous lesions.

During long term follow-up^[36] (24 mo-extended surveillance), this study showed histologically proven precancerous or cancerous lesions in 4 individuals (5.5%) and additional branch duct IPMN in 5 ones, with a diagnostic yield of up to 12.5%, close to the previous rates reported by the Johns Hopkins and the Rotterdam groups.

In comparison, Poley *et al*^[135], of the Dutch group, published the results of a prospective study using EUS in 44 asymptomatic high risk family members with FPC, BRCA1, BRCA2, or p16 germline mutation carriers, and patients with PJS. They found asymptomatic PDAC in three patients (6.8%, two with lymph node metastases), and seven IPMNs (16%). Their high yield (22.7%) may be related to the selection of known carriers of mutations at high risk to develop pancreatic cancer with a higher fraction of individuals at elevated risk.

Nevertheless, it has to be pointed out that IPMNs in both German study and in the Dutch study are EUS-diagnosis, not histologically confirmed. The 12.5% and 16% results may as well represent overestimations.

COST EFFECTIVENESS

A screening test can be considered successful if the benefits/costs ratio is favourable. As previously reported, a EUS-based screening allows an early diagnosis of PDAC, while it is not still clear if this approach could be considered cost-effectiveness.

Rulyak *et al*^[137] compared one-time EUS-based screening to no screening in a hypothetical cohort of 100 members 50 years old of FPC kindred. The life time medical costs and life expectancy were compared, assuming a 20% prevalence of pancreatic dysplasia and 90% sensitivity of EUS and ERCP. They demonstrated that endoscopic screening of these individuals increases patient life expectancy (38 years, similar to other common preventive medical interventions) in a cost-effective manner (\$16885 per life-year saved on the base-case ICER, an indicator which take into account the third-part payer and the societal perspectives). Only patients with a pre-test probability of pancreatic dysplasia of 16% or greater and individuals under 70 years of age seem to have benefits from this approach. Moreover, the sensitivity of EUS and ERCP must be at least 85% in order for screening to be effective. The cost-effectiveness of repeated screening was not determined.

In contrast, Rubenstein *et al*^[138] have performed a clinical and economic evaluation of EUS for 45 years-old male first degree relatives with chronic pancreatitis diagnosed by EUS on screening exam. They compared 4 strategies: do nothing, prophylactic total pancreatectomy, EUS and EUS-FNA and assessed mortality, quality of life, complications and costs. They addressed the inferiority of EUS compared to a no-screening approach because of the low sensitivity of EUS in the presence of chronic pancreatitis-like changes. EUS-FNA provided intermediate results. The prophylactic total pancreatectomy could be considered the better approach in terms of life expectancy if the lifetime risk of pancreatic cancer is

46% or greater.

These studies are based on one-time screening and so are not applicable to individuals who require repeated screening examinations during their life. A review conducted by Latchford *et al.*^[139] focused on a cost-effectiveness analysis of a screening program in PJS, based on EUS and ERCP for molecular analysis of pancreatic juice. According to this review, patients with suspicious findings would be offered CT, all others should repeat screening 1-3 years later, based on risk stratification determined by molecular tests. With this approach over a 35-year period of annual EUS, 3780 screens would be carried out and only those with morphological changes found on EUS are offered CT and ERCP.

This model can give an estimate of costs of about \$372708 per life saved. This cost could be further reduced to \$297000 per life saved by molecular analysis of pancreatic juice. In this case, in fact, most individuals would only be screened every 3 years thanks to more accurate risk stratification.

FUTURE PERSPECTIVES

In the near future, the development of EUS technology should help us to screen HRIs.

Contrast-enhanced harmonic endoscopic ultrasonography (CH-EUS) visualizes parenchymal perfusion in the pancreas without Doppler-related artifacts^[140,141]. It could play a central role associated to EUS-FNA when the latter gives a negative finding in a suspected lesion. Two recent studies^[141,142] showed a higher sensitivity of CH-EUS compared to EUS-FNA for the identification of pancreatic carcinoma. Most of false-negative EUS-FNAs resulted to have a hypoenhancement on CH-EUS examination. Moreover, Kitano *et al.*^[142] found that CH-EUS when combined with EUS-FNA is able to increase the sensitivity from 92.2% to 100% and is superior to MDCT in diagnosing small (< 2 cm) carcinomas, identifying 9 tumours missed by MDCT. Fusaroli *et al.*^[143] also reported that CH-EUS allowed the detection of small lesions in patients with uncertain EUS findings because of chronic pancreatitis. In addition, CH-EUS allows to focus on the lesion target for EUS-FNA.

Diagnostic accuracy of EUS-FNA will be also enhanced by the detection of DNA abnormalities as k-ras point mutations and microsatellite losses^[144,145] or novel protein markers such as mesothelin^[146,147] and prostate stem cell antigen^[147]. Their detection in EUS-FNA specimens may provide confirmation of the presence or absence of malignancy and should negate the need for further testing.

Characterization of pancreatic cysts has become essential for definitive surgical treatment or ongoing surveillance. However, current diagnostic methods (cross-sectional imaging, EUS, and fluid analysis including cytology, fluid characteristics, chemistry, and tumor markers) do not allow an accurate differentiation between the various types of cysts^[148,149]. A novel needle-based confo-

cal laser endomicroscopy (nCLE) miniprobe that can be passed through a 19-G EUS-FNA needle enables real-time imaging with microscopic detail. A pilot study^[150] suggests that nCLE can detect mucinous pancreatic neoplasms with excellent specificity and PPV (100% for both of them) but a low sensitivity and NPV (59% and 50%, respectively) with an overall complication rate of 9%.

Finally, computer-aided diagnostic techniques, yet used in some screening programs^[151,152], could be added to standard EUS images for the differentiation of pancreatic carcinoma from chronic pancreatitis^[151,153]. With digital image processing and computer-aided EUS image differentiation technologies, physicians could use the computer output as a "second opinion" and make the final decisions as reported by the high diagnostic accuracy (98%) of a recent study^[154].

CONCLUSION

These data demonstrate that screening with EUS, preferably associated with MRCP, as reported by International Cancer of the Pancreas Screening summit (83.7% agree for EUS and 73.5% agree for MRI/MRCP)^[96] is feasible and can detect curable pancreatic neoplasms in correctly identified asymptomatic at-risk patients. In particular, as reported by Ludwig *et al.*^[155], EUS could be subsequent to an MRCP as initial imaging. This approach should reduce the number of false positives (patients with abnormal MRCPs who on EUS had no appreciable lesion) avoiding unnecessary surgery. The two modalities may complement each other. In fact, MRI/MRCP, in contrast with EUS, is able to image the entire abdomen and pelvis, an useful feature for patients at risk for multi-organ cancer, but has a low sensitivity in detecting PanIN lesions and small (< 1 cm) pancreatic cancer, even if recently there has been the development of 3T MRI scanners able to detect small tumors in asymptomatic patients through indirect signs (black and white sign) and cystic lesions ≥ 3 mm^[99,156]. MRCP is superior to EUS in delineating lesions involving the pancreatic ductal system^[97,98] even if a recent study^[157] has shown similar results between three dimensional CEUS and MRI in evaluating IPMNs smaller than 1 cm. Nevertheless EUS can image mural nodules associated with increased risk of malignancy.

It is also strongly suggested that surveillance programs should be performed by a center with experience in the specific pathology within the context of peer reviewed protocols to reduce interobserver disagreement^[100].

Indeed, EUS is an operator-dependent technique that requires considerable skills and training in EUS is essential to gain experience to reliably examine the pancreas. The intensity and length of training, the requisite curriculum and the minimum number of procedures required to ensure competency are not well-defined^[158].

Some experts recommend a minimum of 75 pancreatobiliary procedures and 25 cases of pancreatic FNA^[159], others suggest a minimum of 30 supervised EUS-FNA

on pancreatic lesions^[160] while someones believe that the majority of trainees will require double the number of proposed procedures to achieve competency in EUS^[161,162].

An extensive use of CT or ERCP should be avoided in screening programs that require repeated exams in healthy individuals who have only a statistical risk of cancer.

However, a number of questions remain to be answered. What are the significance and natural history of EUS-detected chronic pancreatitis-like abnormalities? What is the clinical significance of PanIN with moderate dysplasia? Should it always be treated with pancreatectomy? How to manage the IPMN-like cystic lesions frequently found in HRIs? Should be offered surgery or a wait-and-see policy can be adopted?

As the resolution of imaging improves and as our knowledge of precursor lesions grows, we believe that these questions will be answered in the future.

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