

Methods and outcomes of screening for pancreatic adenocarcinoma in high-risk individuals

Gabriele Capurso, Marianna Signoretti, Roberto Valente, Urban Arnelo, Matthias Lohr, Jan-Werner Poley, Gianfranco Delle Fave, Marco Del Chiaro

Gabriele Capurso, Marianna Signoretti, Roberto Valente, Gianfranco Delle Fave, Digestive and Liver Disease Unit, S. Andrea Hospital, University Sapienza, 00199 Rome, Italy

Marianna Signoretti, Jan-Werner Poley, Departments of Gastroenterology and Hepatology, Erasmus MC, University Medical Center, 3015 CE Rotterdam, The Netherlands

Roberto Valente, Urban Arnelo, Matthias Lohr, Marco Del Chiaro, Pancreatic Surgery Unit, Division of Surgery, CLINTEC, Karolinska Institutet at Karolinska University Hospital, SE-171 76 Stockholm, Sweden

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Correspondence to: Gabriele Capurso, MD, PhD, Digestive and Liver Disease Unit, S. Andrea Hospital, University Sapienza, Via di Grottarossa 1035, 00199 Rome, Italy. gabriele.capurso@gmail.com
Telephone: +39-6-33775691
Fax: +39-6-33775526

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is a lethal neoplasia, for which secondary prevention (*i.e.*, screening) is advisable for high-risk individuals with "familial pancreatic cancer" and with other specific genetic syndromes (Peutz-Jeghers, p16, BRCA2, PALB and mismatch repair gene mutation carriers). There is limited evidence regarding the accuracy of screening tests, their acceptability, costs and availability, and agreement on whom to treat. Successful target of screening are small resectable PDAC, intraductal papillary mucinous neoplasms with high-grade dysplasia and advanced pancreatic intraepithelial neoplasia. Both magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) are employed for screening, and the overall yield for pre-malignant or malignant pancreatic lesions is of about 20% with EUS and 14% with MRI/magnetic resonance colangiopancreatography. EUS performs better for solid and MRI for cystic lesions. However, only 2% of these detected lesions can be considered a successful target, and there are insufficient data demonstrating that resection of benign or low grade lesions improves survival. Many patients in the published studies therefore seemed to have received an overtreatment by undergoing surgery. It is crucial to better stratify the risk of malignancy individually, and to better define optimal screening intervals and methods either with computerized tools or molecular biomarkers, possibly in large multicentre studies. At the moment, screening should be carefully performed within research protocols at experienced centres, offering involved individuals medical and psychological advice.

Key words: Endoscopic ultrasound; Pancreatic cancer; Screening; High-risk individuals; Magnetic resonance

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Core tip: Screening for pancreatic cancer is advisable for high-risk individuals. There is limited evidence regarding the accuracy of screening tests, their acceptability, costs and availability, and agreement on whom to treat. Successful target of screening are small resectable pancreatic ductal adenocarcinoma, intraductal papillary mucinous neoplasms with high-grade dysplasia and advanced pancreatic intraepithelial neoplasia. Both magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) are employed for screening, and the overall yield for pre-malignant or malignant pancreatic lesions is of about 20% with EUS and 14% with MRI/magnetic resonance colangiopancreatography. However, only 2% of these detected lesions can be considered a successful target. It is crucial to better stratify the risk of malignancy individually, and to better define optimal screening intervals and methods.

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INDICATION FOR SCREENING FOR PANCREATIC ADENOCARCINOMA: WHICH PATIENTS SHOULD RECEIVE SCREENING AND WHICH LESIONS ARE WE LOOKING FOR?

Pancreatic ductal adenocarcinoma (PDAC) is the most common and lethal type of neoplasia occurring in the pancreas. Its incidence has progressively increased in Western countries, possibly due to changes in lifestyle^[1]. The prognosis of PDAC is dismal, due to delayed diagnosis, biological aggressiveness and poor response to medical treatment^[1,2]. PDAC is going to become the second cause of cancer-related death in the United States by 2030^[2].

Prevention, therefore, seems one of the few reasonable approaches to tackle this deadly disease. Primary prevention, consisting of policies aimed at reducing the risk related with modifiable factors, such as cigarette smoking or overweight, is of paramount importance and might reduce substantially the incidence of PDAC^[3].

On the other hand, secondary prevention (*i.e.*, screening) is not advisable for the general population, as the overall lifetime risk of developing PDAC is relatively

low, being close to 1%. PDAC, indeed, does not meet some of the criteria set by the World Health Organization for considering a population screening worthwhile^[4], such as being the target disease a common form of cancer, although it does have a high associated morbidity or mortality. Moreover, screening for cancer is justified if there is an acceptable, safe and relatively inexpensive test procedure and if an effective treatment, capable of reducing morbidity and mortality, is available.

With regards to PDAC, there is limited evidence regarding the accuracy of screening tests, their acceptability, costs and availability, and agreement on whom to treat on the basis of screening results. Furthermore, as the accuracy of a given test also relies on the prevalence of the disease (pre-test probability), it is clear that screening is only advisable for specific population groups with a significantly increased risk of developing PDAC.

With regards to which individuals should undergo screening for early diagnosis of PDAC there is good general agreement among experts. The members of the International Cancer of the Pancreas Screening Consortium (CAPS)^[5] have recently stated that screening is indicated for: (1) Individuals with "Familiar pancreatic cancer" (FPC), without a defined genetic syndrome, but with two or more blood relatives affected by PDAC, of whom at least one first degree relative (FDR); and (2) As far as regards known genetic syndromes, screening is indicated for all patients with Peutz-Jeghers syndrome regardless of family history of PDAC, while for p16 [familial atypical multiple mole melanoma syndrome (FAMMM syndrome)], BRCA2, PALB and hereditary non-polyposis colorectal cancer mutation carriers, screening is indicated only if one FDR or two family members are affected by PDAC.

It is more difficult to agree on which lesions should be considered the target of screening examinations. Ideally small cancerous lesions (T1) amenable for surgery should be diagnosed in due time and receive appropriate treatment, and individuals with clear macroscopic preneoplastic lesions, such as intraductal papillary mucinous neoplasms (IPMNs), might also be considered for surgery depending on size and other cyst features. However, there is no evidence suggesting that cystic lesions should be treated differently than in sporadic cases^[6-8]. The possibility to recognize and the need to treat microscopic preneoplastic lesions such as pancreatic intraepithelial neoplasia (PanIN), whose presence might be indirectly suspected at screening examinations by signs of chronic pancreatitis, is less clear. Advanced PanINs (grade 3) might be considered an appropriate target for screening, while PanIN1 and 2 are extremely common findings in healthy subjects, with their prevalence increasing with age. The yield of "successful" screening examinations should therefore be considered in terms of detection and indication for surgery of lesions such as small, resectable PDAC, PanIN3 and IPMN with high grade dysplasia^[5].

Finally, no imaging modalities gained a univocal evidence-based consensus for screening high-risk indivi-

duals (HRI) for pancreatic cancer, and both magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) have been proposed to be the first line modalities in terms of accuracy.

The present review article will discuss critically the rationale for the use, and the yield of EUS and MRI for detecting solid malignant and premalignant (solid or cystic) pancreatic lesions, and the outcome of surgery in this setting, in order to try to highlight the clinical impact of the screening policies.

EUS

EUS has emerged as an accurate imaging modality for the study of the pancreatic diseases providing high-resolution images of the pancreas without the risk of radiation exposure.

The CAPS Consortium suggests that initial screening of the HRIs should include EUS examination, with an agreement exceeding 83%^[5].

EUS is, indeed, an extremely powerful diagnostic method, and is considered the most sensitive technique for the detection and diagnosis of PDAC. The sensitivity of EUS for solid lesions smaller than 2 cm is 93% compared to 53% and 67% of computed tomography (CT) scan and MRI respectively^[9]. Moreover, the high negative predictive value (100%) of EUS for tumor detection suggests that the absence of a focal mass reliably excludes pancreatic cancer^[10].

In the setting of cystic lesions, EUS obtains a good definition of their morphological characteristics, useful for the differential diagnosis and to identify features (mural nodules, wall thickness) associated with an increased risk of malignancy^[11]. It has also been demonstrated that EUS performs better than MRI regarding the early detection of malignancy in patients with IPMN^[12].

Finally, the possibility to perform guided fine needle aspiration (FNA) permits to obtain tissue samples for histopathological characterization of the lesion with low risk of complication^[13]. However, although the sensitivity, specificity and accuracy of EUS-FNA in solid pancreatic masses was found to be high (84.3%, 97%, 84% respectively) the relatively low negative predictive value (64%) does not allow to exclude the diagnosis of PDAC if it is suspected^[14]. The routine use of EUS – FNA in a screening program is therefore questionable.

On the other hand, microscopic precursor lesions of PDAC, such as PanINs cannot be reliably detected with current imaging methods. Some data, however, suggest that EUS might be able to detect parenchymal changes caused by these lesions. In HRIs PanINs are multifocal and might be associated with lobular atrophy of the surrounding parenchyma, but these features are not associated with the grade of dysplasia. The parenchymal changes caused by multifocal PanINs might be visualized at the EUS as chronic pancreatitis-like features (ectasia, irregularity of the duct and/or parenchyma heterogeneity and lobularity) that cannot be differentiated from non-neoplastic alterations^[15].

For all these reasons, EUS has been used in several studies as the baseline screening test for PDAC in HRIs, alone or in combination with other abdominal imaging techniques. The diagnostic yield of this procedure in detecting any lesions – morphologically suspicious or histologically proven to be malignant or pre-malignant – ranged from 2.6% to 46% at baseline evaluation or during the follow-up. However, the actual rate of detected and resected lesions, for which screening might be considered successful, is much lower, as many patients undergoing surgery in these studies had PanIN 1 or 2, or IPMNs without dysplasia or even benign lesions such as serous cystadenomas, and few others were diagnosed with unresectable PDAC (Table 1).

A screening programme based on EUS was first proposed by Brentnall *et al.*^[16] in 1999. A small prospective cohort of 14 patients (kindreds that had two or more members in the last two generations with pancreatic cancer) were evaluated with both EUS and endoscopic retrograde cholangiopancreatography (ERCP) and compared to CT results. The EUS findings were available for 13 of 14 patients and resulted abnormal in 10 (ranging from minimal to marked signs of chronic pancreatitis) at the first examination. Seven patients were treated with total pancreatectomy, with findings of signs of widespread dysplasia, although the grade of such lesions was not clarified in the paper. The diagnostic yield of EUS in this study was very high (46%) but whether resecting such target lesions might be considered a success is unclear given the associated morbidity of total pancreatectomy. Kimmey *et al.*^[17] reported the experience of the same centre, with a similar protocol, a few years later on 46 patients with more than two first or second-degree relatives with PDAC. This second paper seems to include also the patients reported in their pivotal study. Cross-sectional imaging did not detect abnormalities in those patients, while EUS showed signs of chronic pancreatitis in 24 patients, most of them also reporting symptoms such as diarrhoea and diabetes. Twelve patients (including the seven subjects of their first paper) underwent surgery and the histological examination showed widespread dysplasia in all of them. The diagnostic yield of EUS was equal to 26%, yet it is not clear if the operated patients had PanIN3 or lower grades of dysplasia. Notably, these pivotal papers employed ERCP in all screened individuals, and this might have caused some false positive findings, with the addition of possible procedure-related risks.

The pilot study of Johns Hopkins Hospital^[18] enrolled 38 patients with ≥ 2 FDR with PDAC or affected by PJS. EUS was performed as a baseline screening method and in case of abnormalities CT scan and ERCP were carried out. Twenty-nine patients had abnormalities at EUS (12 pancreatic lesions and 17 EUS changes of chronic pancreatitis). FNA was performed in 21 and 3 alterations were found at cytological examinations (1 atypical neoplastic and 2 atypical reactive pancreatic cells). Seven patients underwent surgery, but only one was diagnosed with a T2N1 PDAC and another with multiple PanINs

Table 1 Summary of diagnostic yields of endoscopic ultrasound based protocols for familial pancreatic cancer screening in high risk individuals

Ref.	Patients and syndrome	Diagnostic Yield ¹ of EUS	No. of solid lesions (mass or nodule)	No. of cystic lesions	No. with chronic pancreatitis features	No. with pre/malignant lesions suspected at baseline or FU	Number with histologically confirmed target lesions for which treatment can be considered a success ²
Brentnall <i>et al</i> ^[16]	13 (FPC)	46.2%	-	-	10 (77%)	6 (46.2%)	?
Kimmey <i>et al</i> ^[17]	46 (FPC)	26%	-	-	24 (52.2%)	12 (26%)	?
Canto <i>et al</i> ^[18]	38 (FPC, PJS)	10.5%	12 (31.5%)	-	17 (44.7%)	6 (15.7%)	2/7 patients who underwent resection (1 PDAC, 1 PanIN3)
Canto <i>et al</i> ^[19]	78 (FPC, PJS)	10.2%	8 (10.2%)	9 (11.8%)	61 (78.2%)	8 (10.2%)	3/7 patients who underwent resection (1 IPMN+ca <i>in situ</i> , 1 IPMN + PanIN3, 1 PanIN3)
Poley <i>et al</i> ^[20]	44 (FPC, PJS, FAMM, FBOC, HP, LFS)	22.7%	3 (6.8%)	7 (16%)	3 (6.8%)	10 (22.7%)	3/3 patients who underwent resection (3 PDAC)
Langer <i>et al</i> ^[21]	76 (FPC, FAMM)	2.6%	7 (9.2%)	3 (3.9%)	17 (22.3%)	7 (11.8%)	0/7 patients who underwent resection
Verna <i>et al</i> ^[23]	31 (FPC, FBOC)	22.5%	2 (6.4)	12 (38.7)	9 (29%)	7 (22.6%)	1/5 who underwent surgery (1 PDAC)
Canto <i>et al</i> ^[24]	216 (FPC, FBOC, PJS)	37%	3 (1.4%)	79 (36%)	54 (25%)	79 (37%)	3/5 who underwent surgery (2 MD-IPMN, 1 BD-IPMN + panIN3)
Total	542	22.2%	35 (6.5%)	110 (20.3%)	195 (36%)	135 (25%)	12/542 (2.2%) of total

¹Endoscopic yield is defined as EUS detection of any lesions morphologically suspicious for BD-IPMN or histologically proven (pre) malignant lesion (PanIN ≥ 2 , IPMN and pancreatic adenocarcinoma) at baseline evaluation and, when performed, during the follow up; ²Treatment is considered a success if any of the following lesions is found at surgery: resectable PDAC, MD-IPMN or IPMN with dysplasia, PanIN3. EUS: Endoscopic ultrasonography; FNA: Fine-needle aspiration; FPC: Familial pancreatic cancer; BD: Branch duct; MD: Main duct; IPMN: Intraductal papillary mucinous neoplasm; PDAC: Pancreatic ductal adenocarcinoma; PJS: Peutz-Jeghers syndrome; PanIN: Pancreatic intraepithelial neoplasia; FAMMM: Familial atypical multiple mole melanoma; FBOC: Familial breast ovarian cancer; HP: Hereditary pancreatitis; LFS: Li fraumeni syndrome.

ranging 1-3. The other 5 resected patients had either a borderline IPMN, PanIN2 or benign lesions (serous cystoadenoma). The diagnostic yield of EUS was 10.5%, if one considers borderline IPMN and PanIN2 appropriate targets for screening. The subsequent prospective study conducted by Canto *et al*^[19] screened 78 consecutive HRIs with EUS. In case of abnormal findings at EUS, further evaluations with EUS- FNA/ERCP were performed. In four patients pancreatic malignancy was suspected at baseline screening. The surgical findings were of IPMN with carcinoma *in situ* in one case, and of IPMN with numerous foci of PanIN3 in another, while the other two patients had IPMN with diffuse and multiple PanIN1-2, or diffuse PanIN1-2. During the follow-up, within 1 year, further 4 patients were diagnosed having suspected pancreatic neoplasia, and while 1 had an advanced unresectable adenocarcinoma, the others underwent surgery with findings of PanIN3 in one case, and either IPMN with/without PanIN1-2 in the other cases. Therefore, although EUS diagnosed 7 of 8 pathologically confirmed pancreatic neoplasms (yield of 10.2%), one might discuss that a large part of the resected patients did not have significant lesions, and that, despite the screening process, one lesion was diagnosed at metastatic stage.

Poley *et al*^[20] reported their data of a first-time EUS screening on a prospective study of 44 patients (with a relatively large proportion of carriers of a clearly defined genetic syndrome associated with an increased risk to develop PDAC). In case of EUS abnormalities, CT

or MRI were performed, as well as a multidisciplinary discussion of all the findings. A total of 7 cystic lesions were diagnosed. Their morphological features at EUS examination were typical of IPMN without signs of malignancy (diameter between 4 and 15 mm without solid component or intramural nodules). In this study this was not considered an indication for surgery. Three asymptomatic solid lesions were detected by EUS and, after resection, the histological examination indeed showed adenocarcinoma. The stage of the tumour was T3N1M0 in two patients and T1N0M0 in the other, but even in this case distant metastases were found 16 mo after surgery. The diagnostic yield of EUS in detecting neoplasms in HRIs in this study was 22.7%.

No malignant lesion was diagnosed in the German surveillance program^[21]. This prospective screening study was carried out in 76 HRIs. The imaging procedures performed at baseline were MRI combined with magnetic resonance colangiopancreatography (MRCP) and EUS. A total of 7 suspected lesions were further evaluated with FNA, but none showed cytological alterations. Surgical exploration of the pancreas was performed in 7 individuals, but the histological diagnoses were 3 serous cystoadenomas, 1 PanIN1, 1 PanIN2 and 1 IPMN. The diagnostics yield of EUS in this study was 2.6%, considering as a "successful" target precancerous lesions also the histologically presence of PanIN2 in the pancreatic parenchyma. This low yield compared to the other previous studies could be correlated to a

selection bias of the patients (the study included a large number of patients at moderate risk). The subsequent German study^[22] evaluated 5-year of prospective screening in the HRIs from this same series, showing a higher yield in detection of pre-malignant lesions using EUS and MRI/MRCP as follow-up methods. Further 9 patients underwent surgical resection, with diagnosis of 1 advanced PDAC and 1 PanIN3, with the other lesions being either serous cysts ($n = 3$) or lower grade PanIN or IPMN.

Verna *et al.*^[23] screened a total of 51 HRIs, 31 of them with EUS. The most common abnormal findings, as expected, were parenchymal changes seen in chronic pancreatitis: two patients had a mass lesion confirmed to be PDAC after FNA, one was resectable (2 cm moderately differentiated adenocarcinoma arising from main duct IPMN), and one metastatic to the liver. Five BD (branch-duct) IPMN were diagnosed and in 4 of them surgery was carried out (all of these had BD IPMN with moderate dysplasia and multifocal PanIN2 lesions on pathology). In this cohort study the diagnostic yield was 22.5%, although only one of these lesions might be considered a successfully detected target.

The multicentre prospective cohort CAPS 3 study^[24] enrolled three groups of asymptomatic HRIs (FPC, BRCA and PJS). It is the first blinded study that compared standardized protocol CT, gadolinium and secretin-enhanced MRCP and EUS. Of 226 patients, EUS diagnosed parenchymal and ductal abnormalities (chronic pancreatitis features) in 25%. Surgery was performed in 5 HRIs, and three of 5 them had IPMN with main duct involvement, high-grade dysplasia and/or associated PanIN3. The diagnostic yield in detecting precursor lesions was considered equal to 37%, but the number of significant lesions was relatively low, with few cases with indication for surgery as compared with previous studies.

MRI

MRI is a widely available technique, and when compared to EUS, has the advantages of being non-invasive, less operator-dependent, easier to be compared and reviewed over time by different specialists taking care of the patients. MRI also offers the opportunity to image the entire abdomen and pelvis. This latter aspect is noteworthy, as it might help diagnosing extra-pancreatic neoplasms, which are fairly common in some specific groups of HRI^[25]. Moreover, MRCP provides excellent visualization of the pancreatic and biliary tree and is particularly useful for characterizing cystic lesions such as IPMNs that are the most common precursor lesions diagnosed in HRI^[6,20,26].

Seven papers investigated the use of MRI for the screening of individuals at high risk for developing a pancreatic cancer. The employed methods are extremely heterogeneous in terms of employed MR scanner, acquisition phases, use of contrast agents and use of secretin. The diagnostic yield for the detection of

pancreatic lesions also varies among the different studies (Table 2), ranging from 3.3% to 57.4%^[21,23-25,27-29].

Secretin-enhanced sequences have been used in three of these seven papers^[21,24,29], but its use has not been univocally validated to improve the diagnostic yield of MRCP in this setting. Nevertheless, a recently published paper on patients with a strong family history of pancreatic cancer undergoing a multicenter Cancer of the Pancreas Screening-3 trial (CAPS 3), proved evidences that the use of secretin can improve the visualization of ductal communication of cystic pancreatic lesions^[30].

Some authors decided to use non-contrast MRI protocol for screening, basing on the hypothesis that changes in pancreatic duct and/or focal drop in pancreatic signal would be detectable even without contrast and that these alterations would have triggered further investigations^[28]. Other authors indeed used a contrast-enhanced MRI protocol. The former argued against this latter position because, even if using a contrast enhanced protocol, all pancreatic cancers individuated in screening programmes were advanced and/or metastatic and due to patient's death^[27,28].

The diagnostic yield of MRI varies sensibly among the different studies with a wide range, between 3% and 50%, probably due to the heterogeneity both of investigated populations and screening protocols^[23,25]. The rate of solid lesions found at MRI seems to be low, ranging between 0.4% and 9%^[24,27]. Similar results have been reported for the detection of chronic pancreatitis-like changes, duct ectasia and PanIN lesions, while pancreatic cystic lesions are diagnosed in a higher percentages of patients (2.6%-35.3%)^[21,24,29]. In two series, a percentage of about 3% of patients with non-reproducible alterations has been reported^[21,28].

Recently a series of 40 high risk individuals undergoing a MRI based screening protocol has been published. Patients underwent a baseline secretin-enhanced MRCP and then a yearly MRI imaging in case of negative result or a EUS with FNA/additional CT scan imaging protocol in case of suspicious result. An overall 40% MRI yield was reported (35% IPMNs, 5% PDAC) at a median 1 year follow up. An additional, synchronous PDAC was found during the IPMN follow up. Five patients underwent a surgical resection, all of them with a successful surgical treatment (3 PDAC, 2 IPMNs with indeterminate grade dysplasia)^[30].

COMPARISON OF EUS AND MRI

There are few studies comparing the diagnostic yield of MRI and EUS in screening HRIs, and it is therefore still unclear which is the best method in detecting early stage PDAC and premalignant lesions in these subjects. The CAPS 3^[24] study evaluated, in a blinded fashion, the ability of these two screening methods in detecting pancreatic lesions in HRIs. This study showed a high concordance between the two diagnostic examinations for the detection of any pancreatic lesion (91%). In

Table 2 Summary of diagnostic yield of magnetic resonance imaging based protocols for familial pancreatic cancer screening in high risk individuals

Ref.	Patients and syndrome	Diagnostic Yield ¹ of MRI	No. of solid lesions (mass or nodule)	No. of cystic lesions	No. with chronic pancreatitis features	No. with pre/malignant lesions suspected at baseline or FU	Number with histologically target lesions for which treatment has to be considered a success ²
Langer <i>et al</i> ^[21]	76 (FAMMM, MPCs, FBOC)	23.3%	6 (7.8%)	2 (2.6%)	1 (1.3%)	12 (15%)	1/7 who underwent surgery (1 PDAC)
Vasen <i>et al</i> ^[27]	77 (FAMMM)	20.7%	7 (9%)	Not specified	9 (11.6%)	7 (9%)	4/5 who underwent surgery (4 R0 PDAC)
Ludwig <i>et al</i> ^[28]	109 (FPC)	16.5%	1 (0.9%)	Not specified	2 (1.8%)	18 (17.4%)	4/6 who underwent surgery (2 MD-IPMN, 1 PDAC, 1 PanIn3)
Canto <i>et al</i> ^[24]	216 (PJG, FPC, FBOC)	33.7%	1 (0.4%)	71 (32.8%)	-	45 (20.8%)	3/5 who underwent surgery (1 MD-IPMN + HGD, 1MD IPMN, 1 BD IPMN + PNET + HGD)
Al-Sukhni <i>et al</i> ^[25]	226 (PJG, FPC, FBOC, FAMMM, HP)	50.4%	2 (0.8%)	80 (35.3%)	25 (11%)	5 (2%)	1/4 who underwent surgery (1 PDAC)
Verna <i>et al</i> ^[23]	33 (FPC, FAMMM, FBOC, HNPCC)	3.3%	3 (9%)	7 (21.2%)	1 (3%)	5 (15%)	Not specified how many pathological reports had been previously described in MRI
Del Chiaro <i>et al</i> ^[30]	40 (FPC, BRAC 2, BRAC 1, FAMMM)	40%	3 (7.5%)	14 (35%)	-	4 (10%)	5/5 (3 PDAC: 1 of them T1N0M0, 1 developed on a synchronous BD-IPMN in FU; 2 intermediate grade dysplasia IPMN of which one mixed type and one branch duct)
Total	777	26.8%	23 (2.9%)	174 (22.39%)	38 (4.8%)	96 (12.35%)	18/777 (2.3%) of total

¹MRI yield is defined as detection of any lesions morphologically suspicious for BD-IPMN or histologically proven (pre) malignant lesion (PanIN \geq 2, IPMN and pancreatic adenocarcinoma) at baseline evaluation and, when performed, during the follow up; ²Treatment is considered a success if any of the following lesions is found at surgery: resectable PDAC, MD-IPMN or IPMN with dysplasia, PanIN3. FPC: Familial pancreatic cancer; BD: Branch duct; MD: Main duct; IPMN: Intraductal papillary mucinous neoplasm; PDAC: Pancreatic ductal adenocarcinoma; PJS: Peutz-Jeghers syndrome; PanIN: Pancreatic intraepithelial neoplasia; FAMMM: Familial atypical multiple mole melanoma; FBOC: Familial breast ovarian cancer; HP: Hereditary pancreatitis.

particular, a strong positive correlation was found for the size of the lesions, and a moderate agreement for the number of pancreatic cystic lesion/solid mass was described. MRI better assessed communication of the cyst with the main pancreatic duct, being superior to EUS (53% vs 27%). EUS missed five patients with a cystic lesion seen by MRI (2 of which BD-IPMN) but diagnosed 12 patients with cystic lesions not reported by MRI (3 of which BD IPMN).

A prospective blinded comparison study was conducted by the Rotterdam group and has recently been submitted for publication. A total of 139 high-risk patients were enrolled and screened with both MRI and EUS. There was high agreement regarding location and size of all lesions. Instead, only a moderate agreement (55%) was reached for the detection of the 11 clinically relevant described lesions. MRI was very sensitive for the diagnosis of cystic lesions, while EUS detected two solid lesions that were not found by MRI (one of these was shown to be PDAC). The results of this study suggest that both techniques are useful, and that they might be complementary rather than interchangeable in screening HRIs, with MRI being able to detect cystic lesions better than EUS, but EUS being more accurate for the diagnosis of small solid lesions, which are the primary target of screening.

Thus, even taken for granted the major sensitivity of EUS in detecting small solid pancreatic lesions, one might argue that there are no solid data suggesting that such ability has a beneficial effect on the disease outcome in this setting. On the other hand, MRI with MRCP protocols have reasonably a good accuracy for the detection of

IPMNs, which represent a precancerous lesion, that potentially progress towards pancreatic cancer. Future studies should compare the ability of these methods in a randomized designed study, and their impact on the long-term outcome of screened subjects.

USE OF SERUM CARBOHYDRATE ANTIGEN 19-9 AS A SCREENING TEST

Serum carbohydrate antigen (CA) 19.9 is the most widely used biomarker for pancreatic cancer, and its use is recommended to monitor the response to treatment^[31] in patients who had elevated level before treatment (between 5% and 10% of the general population are unable to express CA-19-9).

However, the dosage of Ca 19.9 in screening asymptomatic population is not recommended. A number of 70940 asymptomatic patients were screened by Kim *et al*^[32] using Ca 19.9 (cut off > 37 U/mL)^[32]. Although it showed an high sensitivity (the CA 19-9 level was increased in all four patients diagnosed with pancreatic cancer), in screening pancreatic cancer in the general population it showed a very poor predictive positive value (0.9%). Similar results were obtained by Chang *et al*^[33] that found high sensitivity and specificity of this biomarker in predicting pancreatic cancer (100% and 92% respectively) but a 0.5% of positive predictive value.

Slightly better results were obtained in screening symptomatic patients (with high prevalence of pancreatic cancer equal to 49%) where it was found an high positive predictive value (71%) using a cut off Ca 19.9

> 40 U/mL^[34].

The diagnostic role of Ca 19.9 in screening HRIs patients was poorly investigated. The serum dosage of Ca 19.9 was carried out in 8 of 14 patient screened by Brentnall *et al.*^[16] and found to be normal in all these patients. Between the patients enrolled by Verna *et al.*^[23] only one had elevated Ca 19.9. This patient was found to have a pancreatic cyst without dysplasia, and Ca 19.9 remained elevated after surgery. In the German study by Langer *et al.*^[21] all but one patient showed a normal Ca 19.9. The imaging examinations did not show any abnormality of the pancreas at the first evaluation and during the subsequent 28 mo of follow up, and after further investigations the cause of elevation of this biomarker remained unclear. Therefore, although data are limited, the dosage of Ca 19.9 doesn't seem helpful during the screening of HRIs.

SURGICAL INDICATIONS AND OUTCOME

Although screening policies for the prevention or early detection of pancreatic cancer have been initiated about 15 years ago, there are still not enough data to generate evidence-based guidelines regarding the role of pancreatic surgery in this setting. In many of the initial studies screening HRIs, indication for surgery was possibly too wide, and many patients undergoing surgery were diagnosed with benign or borderline findings^[16-19]. As discussed above, what makes the current picture more complicated is the definition of the targets for surgery, as reasonable goals of the screening programme are early invasive or resectable pancreatic cancer, high grade dysplasia IPMNs, and PanIN3 lesions, while the significance of other lesions is less clear. The different approaches to screening and treatment of HRIs is reflected in the results from different surveillance programmes. In this view, not surprisingly, the more recent studies, and personal viewpoints now point toward a less aggressive surgical approach, both in terms of timing for surgery and in extent of pancreatic resection^[35].

PanIN lesions are considered detectable by EUS, by some Centers^[19]. Those lesions may appear as parenchymal changes resulting from a lobulocentric atrophy (LCA) that is present in chronic pancreatitis. However, recent studies showed that this association between PanIN and LCA is not clear and for this reason the use of LCA as a target for early detection of pancreatic cancer should be considered with extreme caution. First, PanIN might not be the cause of LCA; second, LCA can be found in other conditions (as aged pancreas); third, the value of low grade dysplasia at FNA can't exclude another area of high grade dysplasia in a distinct area, sometimes distant from the biopsy site, but not associated with LCA, and not visible at EUS^[36]. Furthermore, while the agreement among different operators for the interpretation of EUS findings when a frank solid or cystic lesion is diagnosed is generally good, this is not the case for the diagnosis of chronic

pancreatitis features, where the agreement remains disappointing even after a consensus process^[37].

For all these reasons there is no consensus on surgical treatment of PanIN lesions, and it is questionable whether finding of PanIN1-2 should be considered a success. However, one can assume that histological confirmed PanIN3 lesions should be resected. The extent of pancreatectomy for those patients is not defined, but a radical partial pancreatectomy seems to be the adequate option.

IPMNs are the most frequent finding detected during the screening of HRIs^[35]. Even if the natural history of IPMNs in individuals with family history is not well defined, some data^[38] suggest that the risk to progress to cancer is not higher than that of sporadic cases. However, the IAP guidelines for treatment and follow-up of cystic pancreatic lesions^[8] suggest to shorten follow-up intervals in patients with BD-IPMN and FPC, and more recently the Italian guidelines^[7] have suggested to consider surgery for all IPMNs in the setting of FPC in fit patients. Which surgical procedure should be performed in such cases is also unclear. Notably, it has been reported that in the setting of HRIs, BD-IPMNs are often associated with distant foci of PanIN3^[36], and IPMNs are also frequently multifocal, thus a radical surgical treatment might be a total pancreatectomy. On the other hand, this may often result in an overtreatment. At any rate, such patients should be discussed in highly specialized centers and the indications should also take in consideration patient age and perception of the problem.

The surgical treatment of solid tumors of the pancreas (suspected pancreatic adenocarcinoma) in HRIs, should follow the rules of oncologic surgery^[26]. The initial approach to these patients in Seattle was total pancreatectomy^[16], but this is not supported by evidence and might only be considered in cases with diffuse multiple lesions in the pancreas (for example a solid tumor in the head and IPMN in the tail). Data on post-operative follow-up of HRIs are extremely scanty. It seems reasonable to follow-up HRIs diagnosed with cancer and resected as other sporadic cases. For patients operated for pre-malignant lesions, the pancreas remnant should be followed-up according to the surveillance program for HRIs^[5].

AREAS FOR IMPROVEMENT

Screening for pancreatic cancer or its precursors has an indication in research settings only. As compared with other screening policies for cancers indeed, there are a number of issues that need to be clarified in order to consider screening worthwhile.

The overall yield of screening methods for pre-neoplastic or neoplastic pancreatic lesions in HRIs is of about 20% with EUS and 14% with MRI/MRCP. However, only 2% of the detected lesions might be considered a successful target of screening (Tables 1 and 2), and there are insufficient data demonstrating that resection

of benign or low grade lesions improves survival. Many patients in the published studies, indeed, seemed to have received an overtreatment by undergoing surgery.

In this view, it is crucial to better stratify the risk of malignancy individually, and to better define optimal screening intervals and methods. The use of a computerized risk assessment tool named PancPRO has been proposed and tested in incident cases of PDAC^[39]; similar tools taking into account the role of family history and possibly other factors such as smoking, might help selecting patients at a substantially higher risk. In the future, application of novel methods of molecular analysis might help better select patients for screening, and provide the indication for surgical treatment. Eshleman *et al.*^[40] recently investigated the possible role of KRAS and GNAS mutations in the duodenal juice of PDAC patients and HRIs undergoing screening EUS. As expected, a high percentage of PDAC patients had KRAS mutations, but among screened individuals the presence of KRAS mutations did not discriminate between these with or without lesions. This is most likely due to the fact that KRAS mutations are an early event, already present in PanIN1, which is extremely common in HRIs and does not represent a target lesion for resection. Crnogorac-Jurcevic *et al.*^[41] analysed the gene expression profile of precursor lesions, PanIN2/3 obtained from prophylactic pancreatectomy specimens of FPC from the Seattle-Washington screening program. They found that transcriptomic changes occur during the progression of PanIN to PDAC, not only in the epithelium but also in the surrounding stroma. These findings support the view that early changes in familial cases are similar to those seen in sporadic cases, and might serve as a tool to predict the behaviour of pre-neoplastic changes in HRIs. The possible role of microRNAs, and other biomarkers, has been investigated by Slater *et al.*^[42]. They reported that serum levels of miR-196a and miR-196b were significantly higher in patients with PDAC as compared to controls, but notably, the serum levels of such miRs were also higher in HRIs screened for PDAC with PanIN2/3 lesions than in screened subjects without lesions or with PanIN1 lesions only. These results, if confirmed, might suggest that a panel of miRs might help selecting patients at higher risk of significant findings among screened individuals.

It is also uncertain whether EUS or MRI, or both, should be employed as screening tests, as few studies compared these two methods. It seems that the two techniques might be considered somehow complementary, with EUS being more accurate for solid lesions and MRI for cystic ones. Future studies should also take into account different subgroups of HRIs when establishing screening intervals and modalities. As an example, it has been reported that in individuals with FAMMM (p16 mutation carriers), cystic lesions are less frequent than in FPC, but solid lesions diagnosed as PDAC are far more frequent^[43]. Thus, in p16 mutation carriers a screening with EUS and not with MRI, with closer intervals, might be preferred.

Another intriguing issue regards the diagnosis of other pancreatic lesions at screening. Pancreatic neuroendocrine tumours (PNETs) have been diagnosed in HRIs receiving screening for PDAC, with a prevalence apparently exceeding the expectations^[24,25,27]. It is unclear whether these findings are just occasional, or if PNETs may represent a part of FPC phenotype, as possibly suggested by findings of similar risk factors for the occurrence of PNETs and exocrine neoplasms^[44].

Finally, it also needs to be determined whether screening for pancreatic cancer in HRIs is really cost-effective. In a simulation considering a 20% prevalence of pancreatic "dysplasia" and 90% sensitivity of EUS and ERCP, endoscopic screening was calculated to be cost-effective, but this analysis most likely considered an excess of lesions now considered as successful targets of screening^[45].

Future large collaborative studies are likely to give the answer to many of these open questions but, until then, screening for pancreatic neoplasms in HRI should be carefully performed within research protocols at experienced centres, offering involved individuals medical and psychological advice.

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