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FIELD OF VISION

Asymptomatic pancreatic lesions: New insights and clinical implications

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Abstract

Despite great efforts in experimental and clinical research, the prognosis of pancreatic cancer (PC) has not changed significantly for decades. Detection of pre-invasive lesions or early-stage PC with small resectable cancers in asymptomatic individuals remains one of the most promising approaches to substantially improve the overall outcome of PC. Therefore, screening programs have been proposed to identify curable lesions especially in individuals with a familial or genetic predisposition for PC. In this regard, Canto *et al* recently contributed an important article comparing computed tomography, magnetic resonance imaging, and endoscopic ultrasound for the screening of 216 asymptomatic high-risk individuals (HRI). Pancreatic lesions were detected in 92 of 216 asymptomatic HRI (42.6%). The high diagnostic yield in this study raises several questions that need to be answered of which two will be discussed in detail in this commentary: First: which imaging test should be performed? Second and most importantly: what are we doing with incidentally detected pancreatic lesions? Which ones can be observed and which ones need to be resected?

Key words: Pancreatic cancer; Early-stage pancreatic cancer; Asymptomatic high-risk individuals; Pre-invasive pancreatic lesions; Cystic pancreatic tumors; Screening; Computed tomography; Magnetic resonance imaging; Endoscopic ultrasound

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INVITED COMMENTARY ON HOT ARTICLES

With great interest we noticed the article published by Canto *et al*[1], which investigated the prevalence and characteristics of pancreatic lesions in high-risk individuals (HRI) for pancreatic cancer (PC).

Up to 10% of PC cases are attributed to a familial or inherited predisposition that can substantially increase the risk for PC[2-7]. For example, patients suffering from Peutz-Jeghers syndrome have a 132-fold increased risk for PC[8]. Other genetic predispositions include hereditary pancreatitis (*PRSS1* gene mutations, lifetime risk for PC of up to 40%)[9,10], the familial atypical multiple

mole melanoma syndrome (*p16/CDKN2A* gene mutations, 13-fold to 22-fold increased risk)[11,12], the Lynch syndrome (mismatch repair gene mutations, 8.6-fold increased risk)[13,14], familial adenomatous polyposis (*APC* gene mutations, 4.5-fold increased risk)[15,16], the familial breast-ovarian cancer syndrome (*BRCA1/2* gene mutations, 2.3-fold to 10-fold increased risk)[6,7,17,18], and individuals with a strong history of PC (at least two first-degree relatives with PC, 6.4-fold to 32-fold increased risk)[2,19]. For these, HRI screening programs have been proposed to detect early-stage pancreatic cancers or even pre-invasive lesions, which are potentially curable because once PC progresses into advanced stages the chance for cure decreases abruptly. In the study by Canto *et al*[1], pancreatic lesions were detected in 92 of 216 HRI (42.6%). The confirmed or suspected final diagnosis included branch-duct intraductal papillary mucinous neoplasm (IPMN) (n = 82), combined-duct IPMN (n = 2), main-duct IPMN (n = 4), and pancreatic endocrine tumor (n = 3)[1]. Such a high prevalence of pancreatic lesions is rare but has been reported before by Verna *et al*[20] who detected pancreatic lesions in 11 of 33 HRI (33.3%) and 14 of 31 HRI (45%) by magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS), respectively. A possible explanation for the high diagnostic yield is the high quality of the screening tests and the highly experienced team of radiologists and gastroenterologists involved in the diagnostic work-up in both studies. On the other hand, it is well known that the prevalence of pancreatic lesions increases with age. Therefore, the age at which the screening test was performed is crucial. In the study by Canto *et al*[1], the mean age of HRI at screening was 56.1 years which is comparable to other published studies. When compared to individuals in the general population, the baseline diagnostic yield was significantly higher in HRI. Incidental cystic pancreatic lesions can be found in up to 2.8% in the general population[21] and this number will increase with better imaging tests. These findings point towards the importance of screening initiatives for HRI with high-resolution imaging tests but also illustrate the dilemma we are currently facing. The more diagnostic imaging studies we perform, the more lesions we will find - even in asymptomatic individuals without increased PC risk. The question that remains is what to do with these incidental lesions. How accurate is our interpretation of an incidental pancreatic lesion? Which lesions really represent a precursor of PC and will proceed to invasive cancer? How many of these lesions already carry incipient cancer? In 2006, the Sendai consensus proposed guidelines for the management of cystic lesions including IPMN and mucinous cystic neoplasms (MCN), which have been widely adopted[22]. However, the diagnosis and subsequent recommendation for pancreatic resection are based on imaging in combination with fine needle aspiration from cystic lesions and confirmation of the presumed diagnosis can only be made after surgical resection. A recent study published by Correa-Gallego *et al*[23] reported a series of 330 patients with incidentally discovered cystic neoplasms of the pancreas from a high volume center for diseases of the pancreas. One-hundred-thirty-six patients (41%) were operated on at diagnosis. Preoperative and final histological diagnoses were correlated[23]. The accuracy of preoperative diagnoses was only 64% for presumed branch-duct IPMN (32 of 50 cases)[23]. Ten of the 18 patients (20%) had an extension to the main duct leading to the final diagnosis of combined-duct IPMN[23]. The diagnostic accuracy for presumed MCN was also only 60% (18 of 30 cases)[23]. Of all patients who were operated on, 6 had an invasive carcinoma (2 branch-duct IPMN, 3 main-duct IPMN, and 1 MCN) and 19 patients had a carcinoma in situ (8 main-duct IPMN, 8 cystic pancreatic endocrine neoplasms, and 3 others)[23]. Therefore, correct interpretation of pancreatic lesions is still problematic and even with established guidelines choosing the adequate treatment remains challenging because the final diagnosis can only be verified after surgical resection.

Another problem is that IPMN are usually multifocal which has been addressed by the concept of the field defect of pancreatic duct instability[24-27]. Pancreata which harbour an IPMN are at increased risk of developing carcinoma. Several studies of patients with IPMN reported synchronous or metachronous invasive PC and these cancers were also present in areas distant from the index IPMN[28-30]. The most recent study by LaFemina *et al*[31] analyzed the prevalence and site of PC progression in 157 patients with suspected or confirmed IPMN who were initially selected for radiographic surveillance. After a median length of surveillance of 15 mo (range: 6-193 mo), 97 patients (62%) eventually underwent resection[31]. Surgical pathology confirmed 18 cases of invasive carcinoma (11%), which were diagnosed at a median of 24 mo after the initial diagnosis of IPMN[31]. Ten patients had main-duct IPMN (56%), 5 had branch-duct (28%), and 3 had combined-duct (17%) IPMN[31]. Four patients (22%) developed PC in a region of the pancreas distinct from the radiographically identified IPMN[31]. Miller *et al*[32] followed 153 patients after pancreatic resection for IPMN with clear resection margins. The authors found that 31 patients developed de novo IPMN in the pancreatic remnant and in 3 cases an invasive carcinoma was diagnosed[32]. Therefore, the confirmation of IPMN requires continuous surveillance of the entire pancreatic gland or of the pancreatic remnant after previous resection[32].

In this regard, Canto *et al*[1] attempted to answer the question of which imaging test should be performed for screening HRI and compared computed tomography (CT), MRI and EUS for detecting pancreatic lesions. The authors found that EUS and MRI detected pancreatic lesions better than CT[1]. The baseline diagnostic yield for EUS, MRI, and CT was 42.6%, 33.3% and 11%, respectively[1]. The authors' conclusion that EUS and MRI are currently the best initial tests for detecting early pancreatic lesions is supported by other studies[33-37]. Main limitations of CT include not only its poor sensitivity for small pancreatic lesions (< 10 mm) which

is important for screening for early pancreatic neoplasms but also the use of ionizing radiation which has recently raised concerns regarding the increased risk of radiation-related cancers associated with CT[38]. However, multi-detector CT remains the most widely used imaging modality because of its high accuracy for detecting solid tumors and staging of pancreatic malignancies, its cost effectiveness and its non-invasive nature. Furthermore, EUS and MRI are more cost-intensive and both tests are more dependent on the experience of the performing and diagnosing gastroenterologist and radiologist. Although the invasive nature of EUS as an endoscopic procedure further limits its role in a screening program, the possibility of EUS-guided fine-needle aspiration of pancreatic cystic lesions may be of diagnostic value especially when malignant cells can be detected. Future work with molecular analysis of cyst fluid, direct cystoscopy, and confocal laser endomicroscopy may further enhance its diagnostic accuracy[39].

Based on the high diagnostic yield of modern high-resolution imaging tests, it appears to be reasonable to routinely screen HRI. Based on current evidence, MRI (and EUS) should be the initial imaging tests to be performed. The question at what age screening of HRI should start has yet to be answered.

Although we have learned a lot in the past two decades about the nature especially of pancreatic cystic lesions, we are still facing a great challenge of how to manage incidental pancreatic lesions. Canto *et al*[1] suggest that the goal of PC screening and surveillance programs should be to detect and selectively treat asymptomatic high-grade precursor neoplasms rather than focussing on detection of invasive cancers. However, especially because IPMN constitute a heterogeneous group of pancreatic cystic neoplasms, a better understanding of the natural history of IPMN and its subtypes is necessary to distinguish lesions that need immediate surgical resection and those that can be safely observed. Not only a better understanding of patient characteristics and further progress in imaging tests are needed but also the identification of reliable biomarkers that can be used to identify pancreatic lesions that are about to proceed to PC in asymptomatic individuals.

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