Editorial

Pancreatic cancer screening: are we almost there?

Ana Garcia Garcia de Paredes, Enrique Vazquez-Sequeiros

Gastroenterology and Hepatology Division, University Hospital Ramón y Cajal, IRYCIS, Madrid, Spain

Correspondence to: Enrique Vazquez-Sequeiros, MD, PhD. Carretera de Coplmenar Km 9.100, Madrid 28034, Spain. Email: evazquezse@gmail.com.

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Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related deaths in the United States and Europe (1). Symptoms are unusual at the early stages, and PDAC is most commonly diagnosed when it is at an incurable stage with only 15–20% of pancreatic cancers resectable at diagnosis (2). Despite improvements in medical and surgical management, PDAC is the only cancer whose mortality has not decreased in recent years (3). The median survival of patients with PDAC is 6 months, with a 5-year survival rate that remains extremely low (8.5%) (1). The first question that comes to mind after reading this data would be, is there anything we can do at present to improve this dreary prognosis? An early disease stage at diagnosis that allows curative intent surgery shows a markedly better survival rate, and provides the best opportunity of achieving long-term survival. Therefore, the best strategy currently available to improve outcomes in patients with PDAC is to develop effective screening protocols to help identify more patients who have it early on.

Several criteria must be met to consider screening for a disease: the disease must be an important and prevalent health issue, precursor lesions must be detected during an early asymptomatic stage, testing for the disease must be suitable to the population screened, and effective treatment should be available (4). Population-based screening of pancreatic cancer is not recommended, due to its relative low incidence, along with the invasive nature of some of the screening modalities, as well as the morbidity associated with pancreatic surgery, and the globally poor survival results. Hence, efforts have focused on the identification of individuals who are at high risk for PDAC based upon family history, or an identified genetic predisposition who may potentially benefit from screening. Approximately 10% of PDAC cases have a familial aggregation (5), and although only a small number of PDAC are hereditary, genetic predisposition entails higher risk than environmental factors (6). In 2013, the International Cancer of the Pancreas Screening (CAPS) consortium published some consensus guidelines regarding pancreatic cancer screening. The guidelines were on evaluating who should be screened, how screening should be performed and how to define success from PDAC screening. The guidelines recommend screening for the following high-risk groups of patients: familial pancreatic cancer, (individuals with ≥2 first degree relatives with PDAC not associated with a genetic syndrome, and taking into account that the risk increases with the number of affected relatives) and genetic predisposition syndromes like, hereditary pancreatitis (*PRSS1*) and inherited cancer susceptibility syndromes with confirmed germline mutations (hereditary breast-ovarian cancer syndrome (*BRCA1*, *BRCA2* and *PALB2*), familial atypical multiple mole and melanoma syndrome (CDKN2A or p16), Lynch syndrome, ataxia telangiectasia (*ATM)* and Peutz-Jeghers syndrome (*STK11))*. Cost-effectiveness studies of screening high-risk individuals have shown positive results (7).

Complete pancreatic resection is the only method to assure survival for patients at risk of pancreatic cancer. However, its long-term consequences prevent this strategy. Since prophylactic total pancreatectomy is not recommended, the aim of PDAC screening is to detect early-stage pancreatic cancer, and high risk premalignant conditions, in order to treat them before the development of an invasive carcinoma. The natural history of PDAC comprises a sequence from dysplasia, to invasive adenocarcinoma. There are three well recognized precursor

lesions to pancreatic cancer. One, pancreatic intraepithelial neoplasia (PanIN) lesions which progress from low-grade dysplasia (PanIN-1) to high-grade dysplasia, (PanIN-3) and are responsible for the majority of pancreatic tumors. Two, intraductal papillary mucinous neoplasia (IPMN) and three mucinous cystic neoplasms (MCN). Premalignant conditions are more common, more frequently multifocal, and of a higher grade, in high-risk individuals, than in patients with sporadic pancreatic cancer (8). Even though premalignant lesions are quite well defined, they are difficult to detect (especially PanIN, which are typically too small to be visualized by imaging) as well as, their management is not well established.

Screening of individuals whom are at a high risk for PDAC leads to the identification of asymptomatic pancreatic lesions, mostly cysts, in up to 42% of patients (9). However, it is not clear the relevance of these findings, and the management of these lesions, especially cysts, is still a matter of debate since only a few studies have assessed long-term screening programs. In a recently published study, Canto *et al.* (10) evaluated the incidence of pancreatic cancer, and the risk factors for malignant progression from precursor lesions within a large multicentric cohort of 354 high risk individuals whom were enrolled in screening programs (CAPS 1–4 studies) over a 16-year period time. Forty-eight percent of patients had lesions detected at baseline, similar to previous studies (9). One of the fears of pancreatic cancer screening, is a false positive examination, and the risk of overtreatment for benign lesions; a huge risk, taking into account the morbidity of pancreatic surgery, even in experienced centers. The selection of patients for pancreatic surgery in this context is challenging, and still in evolution, as there is a lack of knowledge regarding the risk of progression of these premalignant lesions. Canto *et al.*'s study (10) provides important information regarding the natural history of pancreatic lesions detected at baseline. Neoplastic progression was observed in 7% (14 cases of PDAC and 10 of IPMN with high grade dysplasia or PanIN-3) of the cohort, over the 16-year period of time, and the majority of them (93%) had previously had lesions with worrisome features, (solid mass >5 mm, multiple cysts, cyst size ≥3 cm, thickened/enhancing walls, mural nodule, dilated main duct >5 mm) or rapid cyst growth (>4 mm/year). In fact, presence of multiple cysts (≥3), or a mildly dilated pancreatic duct at baseline, was significantly associated with neoplastic progression. Presence of multiple cysts at baseline has not been previously reported as a predictor of malignant progression in sporadic IPMN (11), which translates the relevance of Canto *et al.*'s findings regarding the fact that cystic lesions in high-risk patients may not have the same natural history of pancreatic cancer than in the general population, and may need a different approach. Also, development of worrisome features, which occurred in 19% of patients undergoing surveillance, was the most robust predictor for developing pancreatic cancer, or high-grade lesions.

How to screen for PDAC is an open question. An ideal screening tool for detecting early cancer should be a noninvasive, sensitive and specific to detect precancerous lesions. Unfortunately, noninvasive methods of pancreatic cancer evaluation such as Ca 19-9 are not sensitive enough for early lesions (12). Computed tomography (CT) is a useful tool for staging pancreatic cancer; however, its role for screening is hampered due to its poor ability to detect small lesions [it hardly detects lesions under 2 cm (13)] and its ionizing radiation nature. Endoscopic ultrasound (EUS) and magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP) are the most employed methods due to their highest yield, and no radiation nature, and they are probably complementary techniques. Even though there is no consensus about which is the best method for screening, and there is few data comparing outcomes from different strategies, in a recent study EUS detected more pancreatic abnormalities than MRI (14). EUS' ability to detect very small pancreatic solid or cystic lesions (it can detect lesions as small as 5 mm), parenchymal heterogeneity, the possibility of tissue sampling of abnormal areas by fine needle aspiration (FNA), with an accuracy of 92% (15) and its low risk of complications, may position this technique as the preferred one. Canto *et al.* (10) reinforced the main role of EUS, in PDAC screening as early stage PDAC was diagnosed by EUS and not by MRI or CT in their study. Optimal intervals for surveillance also need to be determined. Most protocols, including Canto *et al.*'s, follow annual imaging if the pancreas is normal at baseline.

In Canto *et al.*'s work, 71% of asymptomatic PDAC detected during the 16-year period follow-up were resectable at diagnosis, a large improvement if we compare it to the fact that only 20% of sporadic PDAC are resectable at diagnosis. In terms of survival, the results of this study are encouraging as 85% of resectable asymptomatic diagnosed PDAC were alive at 3 years, a much higher rate than observed in sporadic PDAC. There were no cases of mortality among patients diagnosed with high grade dysplasia IPMN or PanIN-3, stressing the importance of

diagnosis at a premalignant stage.

When to begin screening in high risk individuals is another unanswered question. The age to start screening varies in different studies. It has been set at 45 years in some centers and at 40 years or ten years before the youngest age of diagnosis in the family in others. A Dutch study found that screening for PDAC in high risk individuals rarely reveals significant lesions before the age of 50 (16). Also, a recent study that evaluated the usefulness of initial screening of PDAC in patients carrying high-risk mutations found that screening under 50 is of low-yield (14). Canto *et al.* (10) based the screening age on the mean expected age of development of PDAC and the youngest age of onset of PDAC in the family, that is they began screening at age 50 or 55 years or 10 years younger than the youngest relative with PDAC. Only in Peutz-Jeghers they began screening at 30 years. Mean age at baseline was 56 years and malignant progression happened at a median age of 67 years. Age >60 at baseline was significantly associated with neoplastic progression, and median time from baseline screening until PDAC was almost 5 years, strengthening the suitability of their chosen times to start screening and the relevance of long-term surveillance. Interestingly, the median age for development of PDAC in high risk individuals is about the same as that for sporadic PDAC (17). Smoking is a strong risk factor in PDAC (18) and it has also been shown to lower the age of onset (19). Smokers developed PDAC nine years earlier than non-smokers in the Spanish familial pancreatic cancer registry (20), raising the question that, should people who have ever smoked begin screening earlier? Variation in surveillance programs do exist among different centers and the best surveillance protocol remains to be established. It is difficult to determine fixed surveillance protocols, due to the fact that PDAC risk varies among high risk patients.

There are several research programs of PDAC screening in high-risk individuals. The Spanish familial pancreatic cancer registry (Pan-Gem-FAM) was established in 2009 to identify families at high risk of developing PDAC, and enroll them in surveillance programs. Their initial results were published in 2016 (20). The Netherlands used EUS in 44 high-risk patients, finding a 7% pancreatic cancer rate, and a prevalence of 16% for premalignant conditions (21). However, most studies evaluating pancreatic screening, have only reported results of baseline screening. Canto *et al.*'s recent study presents the long-term results of the largest PDAC screening program that was led by John Hopkins University, which included 24 American hospitals. The CAPS consortium established that the aim of a PDAC screening program should be to diagnose, and treat early stage cancers (T1N0M0) and high-grade dysplastic premalignant conditions (PanIN and IPMN). However, there was no agreement regarding when to start screening, screening intervals or how to manage certain lesions. Canto *et al.*'s recent work helps to start answering these questions.

Huge efforts are being made in different fields to improve the abysmal prognosis of pancreatic cancer. Regarding screening, the recent study by Canto *et al.* shows promising results, as it reflects that survival in high risk individuals is increased, and death from PDAC has decreased due to the screening program put in place. It strengthens the previous known facts, that the majority of early localized pancreatic tumors are asymptomatic. Their results are encouraging, as they reveal that continued follow-up of high risk individuals lead to a higher proportion of early detected PDAC, and that earlier detection of pancreatic cancer significantly improved survival. In other words, the key to improve PDAC survival is indeed early detection, and follow-up of high risk individuals appears to be beneficial. Also, this study provides clinically relevant information regarding radiological features that are associated with neoplastic progression that may certainly help us guide the management of detected pancreatic lesions in high risk individuals, which may differ from sporadic lesions. It seems that finally, the light begins to appear at the end of the tunnel in pancreatic cancer, at least in high risk patients.

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