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Pancreatic cancer screening: Still a delusion?

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ABSTRACT

Pancreatic adenocarcinoma represents the fourth most common cause of cancer mortality and death due to pancreatic cancer (PC) have increased since 2003. Its incidence has also raised about 30% in the past decade and it is expected to become the second cause of cancer mortality by 2020 in the USA. Most PC present with metastatic disease and improvements in treatment outcomes for this group have been disappointing. These observations support the idea that screening to identify patients at an earlier stage might be an important strategy in improving overall PC outcomes. Many protocols have been tested, nevertheless, by now there is no effective screening program.

Given the overall low incidence of disease and the current lack of accurate, inexpensive and noninvasive screening tests, the consensus is that widespread population-based screening for PC in the general population or in patients with only one affected first-degree relative is neither practicable nor indicated in most countries. However, a different scenario is screening patients with higher risk for PC, most of them with hereditary conditions predisposing the development of this neoplasia. In fact, some guidelines are now available helping to select these individuals at risk and to screen them, in order to achieve early detection of PC.

Introduction: the facts

Pancreatic ductal adenocarcinoma (PDAC) represents only 3% of estimated new cancer cases each year, nevertheless it is the fourth most common cause of cancer mortality with 48,960 new cases and 40,560 deaths estimated in 2015 [1]. As a matter of fact, contrary to the death rates for other leading causes of cancer death (lung, colorectal, breast and prostate), which have declined since 2003, the death rate from PDAC has increased during the same time period [2]. Its incidence has also raised about 30% in the past decade and it is expected to become the second cause of cancer mortality by 2020 in the USA [1].

As pancreatic cancer (PC) typically develops with few symptoms, only 10–20% of the patients are diagnosed at a stage amenable to resection, the only possibility of cure. Therefore, it has a poor overall five-year survival rate of 5% combining all stages, with a survival rate of about 20% and 2% for patients with localized disease and with distant metastases, respectively [3].

Over the last decades, there have been remarkable improvements in medical and cancer care. Nonetheless, these advances have only had a small beneficial impact for PC patients. The one-year survival rate for all stages has increased from 15% (between 1975 and 1979) to 21% in 2013 [4]; and five-year survival has increased from 2.5% (between 1975 and 1979) to only 7.2% (between 2005 and 2011) [4].

These survival improvements have been attributed mainly to an increased use of axial imaging techniques together with a decrease in surgical morbidity and mortality rates [5]. Patients with PDAC discovered by chance through imaging (pancreatic incidentalomas) appear to have increased survival rates. Winter et al. [6] depicted that patients with pancreatic incidentalomas had a median survival of 30 months vs. 21 months in those with carcinoma found after symptoms appearance, corroborating the idea that earlier diagnosis can lead to an improved outcome. Unfortunately, few cases of PC are diagnosed by chance. In one study during 8 years of follow-up, 24 out of 321 patients (7%) with a solid pancreatic mass had their diagnosis performed incidentally, and 58% of them were adenocarcinomas [7].

Most PC present with metastatic disease and improvements in treatment outcomes for this group have been disappointing.

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Abbreviations

PC	pancreatic cancer
PDAC	pancreatic ductal adenocarcinoma
FDR	first-degree relative
PanIN	pancreatic intraepithelial neoplasia
IPMN	intraductal papillary mucinous neoplasm
PJS	Peutz–Jeghers syndrome
EUS	endoscopic ultrasound
CT	computed tomography
MRI	magnetic resonance imaging
ERCP	endoscopic retrograde cholangio-pancreatography
PET	positron emission tomography
MRCP	magnetic resonance cholangio-pancreatography
HRIs	high-risk individuals
CA 19-9	carbohydrate antigen 19-9
MCN	mucinous cystic neoplasm
MD-IPMN	main duct intraductal papillary mucinous neoplasm
BD-IPMN	branch duct intraductal papillary mucinous neoplasm
FPC	familial pancreatic cancer
HBOC	hereditary breast and ovarian cancer syndrome
DM	diabetes *mellitus*
MCDT	multidetector computed tomography
MiRNA	microRNA
GPC1	glypican-1
CrExos	circulating exosomes
FAMMM	familial atypical multiple mole melanoma
DWI	diffusion-weighted imaging
MMR	mismatch repair
CAPS	Cancer of the Pancreas Screening
CEUS	contrast-enhanced ultrasound
CEA	carcinoembryonic antigen

Patients with advanced stage tumors have been typically treated with gemcitabine, which increases the median survival to 6 months from an untreated median survival of 3 months [8,9]. Numerous randomized controlled trials studying outcomes with novel chemotherapy agents and combinations (such as FOLFIRINOX) with good biologic rationale have been recently published, but median survival has not increased substantially beyond 6 months [8,10–20]. It is remarkable that with substantial effort and commitment to clinical trials, little has been gained in overall survival in metastatic PC. Regarding adjuvant treatment after resection of PDAC, a recent multicentre, open-label, phase 3 randomized clinical trial (ESPAC-4 trial) showed that the combination of gemcitabine and capecitabine was superior to gemcitabine on monotherapy and should be the new standard of care in this scenario [21].

These observations support the idea that screening to identify patients at an earlier stage might be an important strategy in improving overall PC outcomes. Many protocols have been tested, although, at this time, there is no recognized effective screening program.

The great majority of PCs, at least 90%, are considered sporadic [22–24]. Bearing in mind that PC is a rare disease, the detection rate in average risk population is low. As a matter of fact, in a screening study that included 2511 patients, only 5 cancers were detected by magnetic resonance imaging (MRI) combined with US (a detection rate of 0.20%) [25].

Given the overall low incidence of disease and the current lack of accurate, inexpensive and noninvasive screening tests, the consensus is that widespread population-based screening for PC in the general population or in patients with only one affected first-degree relative (FDR) is neither practicable nor indicated in most countries [26].

However, a different scenario is screening patients with higher risk for PC, most of them with hereditary conditions predisposing the development of this neoplasia. In fact, some guidelines are now available helping to select these individuals at risk and to screen them, in order to achieve early detection of PC [27]. Unfortunately, these individuals represent only a minority of all PCs, being the burden of sporadic cases the true enemy that should be intensively studied to help physicians reduce PC-related mortality in a near future [5].

Natural history: a window of opportunity for early detection?

PC typically develops with few symptoms that vary according to tumor location. When symptoms are present, a characteristic pattern of painless jaundice is often recognized. However, commonly atypical patterns of symptoms such as weight loss, abdominal pain and malaise might lead to delays in diagnosis. Also, most patients present with metastatic disease, when treatment is disappointing. On the other hand, many patients initially thought to have localized and resectable cancer (10–20%) will die from recurrent or metastatic disease [5]. Despite all these adverse facts, whether the dismal prognosis of patients with PC compared to those with other types of cancer is a result of late diagnosis or early dissemination of the disease, is still unknown.

A recent study from Yachida et al. [28] suggests that there may be a large window of opportunity in the natural history of PC for its detection while the disease is in its earliest and treatable stages. In this study, genomic sequencing was performed on cancer cells obtained at autopsy from seven PC patients. Data was generated by sequencing the genomes to evaluate the clonal relationships among primary and metastatic cancers. The authors performed a quantitative analysis of the timing of the genetic evolution of PC, concluding that at least a decade between the occurrence of the initiating mutation and the birth of the parental, non-metastatic founder cell is necessary. Yachida et al. [28] based on the differential accumulation of mutations in primary and metastatic lesions estimated an average of 11.7 years elapsed from tumor initiation to overt cancer development and calculated an average of 6.8 years elapsed between the development of overt cancer and the development of metastatic ability. This finding that pancreatic tumors are present for a significant period of time before clinical manifestation emphasizes the potential of screening for early detection of PC.

All these data provide novel insights into the genetic features underlying PC progression and define a broad time window of opportunity for improving outcomes through identification of the disease, when treatments are likely to have a benefit, assuming suitable biomarkers can be found that correspond to the pre-cancerous or pre-metastatic time periods.

Screening goals

The ultimate goal of a cancer screening program is to improve survival rates. PC patients detected in early localized stage (stage I), amenable to R0 resection, have an estimated survival no longer than 24 months. Taking this into account, the ideal screening strategy for PC would target high-grade benign noninvasive precursor neoplastic lesions, such as pancreatic intraepithelial