# Pancreatic cancer screening

## *Rastreamento do câncer de pâncreas*

Mônica Soldan[1,2].

When it comes to the world population, the incidence of pancreatic cancer is low, with a cumulative risk of 1% throughout life, not rendering in screening recommendations by the World Health Organization[1]. Pancreatic cancer is the 4th leading cause of death by Cancer in the US, with the prospect of becoming the second in 2030[1]. In Brazil it accounts for 2% of all types of neoplasias and for 4% of all cancer deaths. Although not among the top ten cancers in Brazil, it is the eighth leading cause of cancer death, since most patients are diagnosed in locally advanced or metastatic disease stages. Nevertheless, it holds the 13th position in incidence by type of cancer in the rankings made by the National Cancer Institute of the Brazilian Ministry of Health[2].

The pancreatic ductal adenocarcinoma (PDA) originates in the exocrine pancreas and accounts for 95% of pancreatic tumors. The risk of developing PDA throughout life is 1.49%, or one in 67, and its incidence increases with age[3]. Most diagnoses occur after the age of 50, with a peak incidence around 70 to 75 years, being more common in men. Other risk factors related to pancreatic cancer are smoking, chronic pancreatitis, cirrhosis, obesity, sedentary lifestyle, high fat and cholesterol diet, diabetes mellitus, occupational exposure to carcinogens, Jewish ancestry (Ashkenazi) and low socioeconomic status. The main family syndromes related to the disease are hereditary pancreatitis, hereditary non-polypoid colorectal cancer, hereditary breast and ovary cancer, familial atypical multiple melanoma, Peutz-Jeghers and ataxia-telangectasia[4].

PDA is a disease with high lethality, with a 5% five-year survival rate. Mortality has not changed much in spite of advances in surgical techniques in the last 80 years, after the introduction of pancreatoduodenectomy[3]. Surgical resection is the only potential cure for PDA, but in 80% of patients with symptoms the tumor is already unresectable at the time of diagnosis. Candidates for surgical resection survive on average 12 months, this time being reduced to 3.5 months in those not candidates for surgery[3]. Increased resectability requires the detection of PDA at an early stage, and the selective screening of patients at high risk for its development can be a good way to achieve this goal.

Both genetic and modifiable factors contribute to the development of PDA, and the hereditary component can be identified in 10% of cases, with a specific mutation implicated in 20% of such individuals[3]. Through the identification and screening of patients at increased risk of PDA, the detection of precursor and early lesions (secondary prevention) would come and, as a consequence, there would be an increase in survival among patients undergoing surgical resection.

In 2010, 50 specialists of different specialties from different countries gathered in a consortium to generate guidelines for PDA screening, the CAPS consortium, and this meeting drew some conclusions[5]: screening in the general population is not recommended, as the the disease's cumulative risk is low (1.3%) throughout life; individuals considered to be at high risk for the development of PDA (>5% cumulative lifetime risk or relative risk increased by 5x) should be screened; the main tool used to quantify this risk is family history, the risk stratification being determined by the number of relatives affected and their relationship to the individuals under risk assessment; several genetic tests may identify familial susceptibility, but their role is limited because the genetic basis of PDA is not fully understood and additional genetic testing may be discovered in the near future.

A screening program should aim to identify and treat T1N0M0 lesions with negative margins,

1 - Federal University of Rio de Janeiro, Clementino Fraga Filho University Hospital, Gastroenterology Service, Rio de Janeiro, RJ, Brazil. 2 - São Vicente de Paulo Hospital, Endoscopy Service, Rio de Janeiro, RJ, Brazil.

as well as high-grade dysplastic precursor lesions (intraepithelial pancreatic neoplasia and papillary mucinous intraductal neoplasia).

## Who should be screened?

First-degree relatives of PDA patients belonging to family groups where at least two first-degree relatives are identified with the disease.

Patients with Peutz-Jeghers syndrome (carrying mutations of the STK11 gene) and bearing patients mutation in the p16, BRCA2 and HNPCC genes, with at least one first-degree relative with PDA.

## When to screen?

There is no consensus as to when to start or stop screening, but a slight tendency to recommend its start at age 50. The interval between examinations and the time limit for completing the screening process are also undefined, the currently proposed range being on an annual basis.

## How to screen?

There is consensus that the imaging method to be used is echoendoscopy and/or magnetic resonance cholangiopancreatography. Screening should not be performed with computed tomography or endoscopic retrograde cholangiopancreatography[5].

Studies evaluating the capabilities of echoendoscopy in the screening of patients at risk showed results with great variability (2% to 46%), and when compared with magnetic resonance imaging (MRI), few data are available. Echoendoscopy appears to be superior in the detection of small solid lesions, whereas MRI seems to be better for detection of cystic lesions[1].

Carbohydrate antigen (CA) 19.9 is the most commonly used marker for PDA and its use is recommended to monitor treatment in patients who had high levels prior to treatment. The dosage of CA 19.9 is not recommended, however, for screening of asymptomatic individuals. With a cutoff value > 37U/ml, its positive predictive value is extremely low (around 1%) in the general population, even with high sensitivity and specificity (100% and 92%, respectively)[1]. For the screening of symptomatic patients, for whom the PDA prevalence is around 50%, the predictive value is higher (70%), using a cutoff value of 40U/ml[1].

As a tool for evaluating a good tracking strategy, we could use the following questions:
1 - Does it reach the correct target?
2 - Is it applicable, ie, is the technology involved available and affordable?
3 - Does it increase survival?

The first question's answer is the number of precursor and initial stage lesions submitted to surgical resection. As an example, we can cite the article published by Vasen *et al.*, in 2016[6]. In that study, a cohort with prolonged follow-up time, they detected PDA in 13 of 178 individuals (7.3%) with mutation of the CDKN2A gene (responsible for the production of p16), with resection rate of 75%. Two patients (1%) of the same mutation group underwent resection of low-risk precursor lesions, and patients screened for familial PDA accounted for the resection of 6.1% of the precursor lesions and 1.9% of the high-risk precursor lesions.

An American study analyzing costs per year of added life and national average expenditures based on Medicare[7] found: for Peutz-Jehgers syndrome, US$ 638.62 per year of life added and US$ 2,542.37 national average expenditure; for hereditary pancreatitis, US$ 945.33 and US$ 3,763.44; for familial pancreatic cancer syndrome and p16-Leiden mutations, US$ 1,141.77 and US$ 4,545.45; and for patients with newly onset diabetes over 50 years with weight loss or smoking, US$ 356.42 and US$ 1,418.92.

In response to the third question, we can cite the same article by Vasen *et al*[6], which evaluated a long-term prognosis (>50 months) in a large series of patients (>400). In that study, the five-year survival rate in patients under surveillance who had CDKN2A/p16 mutation and PDA was 24%, a much better result when compared with the typically found PDA 5% survival rate.

The answers to these questions in our midst may take a long time. Multicentric screening protocols observing the aforementioned CAPS Consortium selection criteria, in reference centers, with multidisciplinary teams containing experienced and engaged surgeons would be a good start.

Finally, it is important to emphasize the primary prevention, with health policies that aim to reduce the rates of smoking and obesity, two controllable factors of great impact in the pathophysiology of PDA.

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