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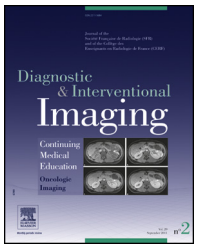

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# Pancreatic carcinoma: Key-points from diagnosis to treatment

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**Abstract** Pancreatic ductal carcinoma is one of the deadliest cancers in the world. The only hope for prolonged survival still remains surgery with complete R0 resection even if most patients will promptly develop metastases and/or local relapses. Due to the silent nature of the disease, fewer than 20% of patients are eligible for a curative-intent resection. As no gain in survival is expected in case of residual tumor, imaging plays a major role for diagnosis and staging to select patients who will undergo surgery. Multidetector-row computed tomography and magnetic resonance imaging are the key stones and radiologists must be aware of imaging protocols, standardized terms and critical points for structured reporting to assess the tumor staging, minimize potential the morbidity associated with surgery and offer patients the best therapeutic strategy.



Pancreatic cancer (PC) is one of the deadliest cancers in the world. To date, surgery still offers the only hope for cure or prolonged survival. Nevertheless, due to the initial silent course and the delayed diagnosis, less than 20% of patients are candidates to surgical resection. Whatever the stage of the disease, imaging is the cornerstone for therapeutic decision and must lead to detailed, objective pretreatment staging. The understanding of tumor and pancreatic anatomical particular features, especially concerning vascular involvement and the knowledge of the lexicon of standardized terms by radiologists are crucial for reporting templates and optimal treatment of these patients.

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## Epidemiology, survival and prognostic factors

PC is a highly aggressive tumor that carries a high mortality rate and is expected to become the second cause of cancer-related death in 2030 [1]. In 2008, the estimated number of cases in Europe was 96,000 with 95,200 deaths and 265,000 deaths in the world, representing the poorest prognostic tumor of the digestive tract [2,3].

Prognosis remains poor due to the high percentage of advanced disease at the time of diagnosis and the limited efficacy of current combinations of drugs and radiation therapy. Despite decades of efforts, the reported 5-year survival was less than 5% in 2005 and the mortality rates remains stable without significant changes. To date, surgery remains the only hope for prolonged survival but even for resected patients, the 5-year survival rate remains approximately 20%, as almost 80% will recur within 2 years of surgical resection [4].

## Histopathology

Invasive pancreatic ductal adenocarcinoma (PDAC), originating from exocrine pancreatic duct epithelioma, represents 95% of malignant pancreatic neoplasms. Ductal carcinomas are characterized by hypovascularisation, marked interstitial fibrosis and desmoplastic reaction, that will explain the imaging protocol for detection. They are also prone to invade nerves, small veins, lymphatic spaces and spread along perineural spaces. All these characteristics will explain peripancreatic and extrapancreatic spread, and favor proximal vascular involvement, lymph nodes and liver metastasis.

As other tumors, invasive PDAC evolves through neoplastic precursors. Premalignant lesions of invasive PDAC include pancreatic intraepithelial neoplasias (PanINs), intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms. PanINs are microscopic lesions with progressive increasing mutations, cytological and architectural abnormalities, classified from PanIN-1 to 3 according to the severity of cytoarchitectural atypias. PanIN-3 lesions are present in 30—50% of pancreata with invasive ductal carcinoma [5]. IPMN are noninvasive mucin-producing cystic neoplasms with potential progression over years from low-grade to high-grade dysplasia and invasive carcinoma. Contrary to microscopic PanINs, IPMNs are increasingly discovered by imaging. Some features are correlated with an increased risk of malignancy. Malignant IPMN are mainly observed in main duct type and a ductal diameter more than 1 cm, the presence of mural nodules and abnormal attenuating area in the adjacent parenchyma are correlated with malignancy. Predictors of malignancy that include obstructive jaundice in case of a cystic mass of the head, enhanced solid components, a main pancreatic duct diameter $\geq$ 10 mm should lead to surgery, while patients with worrisome features such as cyst size $\geq$ 3 cm, thickened enhanced walls, non-enhanced mural nodules, main duct diameter 5—9 mm and stenosis with distal pancreatic atrophy should be evaluated by endoscopic ultrasound (EUS) [6]. The 5-year PC development is approximately 46% for main duct-IPMNs with a disease-specific mortality of 19% in a large series of 285 patients [7—9].

Concomitant but distinct PDAC with IPMN has been reported for years with a frequency between 2.5% to 9.2% [10]. Although not very frequent, as IPMN is easily detected by imaging and especially using magnetic resonance imaging (MRI), it has become a definite potential target for early detection of sporadic PC.

## Risk factors and screening

Advanced age, nicotine exposure (relative risk [RR: 2—3], obesity [RR: 2], long-standing type 2 diabetes mellitus [RR: 2], chronic pancreatitis are identified risk factors of PDAC. Although the cause is multifactorial, cigarette smoking and family history are dominant. Non-hereditary chronic pancreatitis is associated with a RR of 15 [11]. Compared with the general population, individuals with hereditary pancreatitis have an approximately 53-fold increased risk for PC and cumulative rates of PC reach 30 to 40% by the age of 70 years [12].

Main genetic syndromes with higher risk of PDA include genetic pancreatitis, Lynch syndrome, Peutz-Jeghers syndrome, familial atypical multiple mole and melanoma, hereditary breast and ovarian cancer syndromes, hereditary non-polyposis colorectal carcinoma (HNPCC) and familial adenomatous polyposis (FAP).

Case control and prospective cohort studies support the presence of familial aggregation and genetic susceptibility in the development of PC. In familial aggregation forms, more than 2 first-degree relatives or more than 3 whatever the degree is, occurred in a family. The risk increases with the number of cases.

Approximately 5 to 10% of individuals with PC report a history of PC in a close family member. Screening for PC remains a difficult subject. As early stage cancer are potentially curable, screening has been recommended for high-risk individuals. Such a program should detect and treat early PC (T1N0M0) and high-grade dysplastic precursor lesions (PanIN and intraductal papillary mucinous neoplasm). According to a panel of experts, first-degree relatives of patients with PC from a familial PC kindred with at least two affected first degree relatives (FDR), patients with Peutz-Jeghers syndrome, P16, BRCA2 and hereditary non-polyposis colorectal cancer mutation careers with $\geq$ 1 affected FDR are concerned. EUS and/or MR cholangiography are considered accurate to detect small solid and cystic lesions and do not involve ionising radiation. They have been recommended for initial screening. Nevertheless, screening for PC in high-risk individuals highlights numerous questions that have not been answered such as the age for initiate screening, risk of overtreatment especially concerning the risk of pancreatic surgery). Annual evaluation should be performed and shortened to 3 months in case of newly indeterminate solid lesion or duct stricture if surgery is not imminent [13].

## Imaging of PDAC

Imaging of PDAC will have to face 3 challenges: identification of the primary tumor, evaluation of the local resectability and detection of distant metastasis.

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