Pancreatic cancer: Clinical presentation, pitfalls and early clues

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Summary
The diagnosis of pancreatic cancer usually depends upon symptoms; consequently it is late when there is no chance for cure. At this point, pain, anorexia, early satiety, sleep problems and weight loss are present. Back pain also may be prominent, which predicts unresectability and shortened survival after resection. However, earlier recognition of symptoms of pancreatic cancer might improve early detection of the cancer. For example, 25% of patients have symptoms compatible with upper abdominal disease up to 6 months prior to diagnosis and 15% of patients may seek medical attention more than 6 months prior to diagnosis. These symptoms erroneously may be attributed to problems such as irritable syndrome. Symptoms, however, may be less common. For example a quarter of patients with pancreatic cancer may have no pain at diagnosis, and half, particularly those with pancreatic head tumors, may have little pain compared with patients with body-tail tumors. However, if the tumor is suspected because of predisposing conditions, earlier diagnosis may be possible. These conditions include diseases such as chronic pancreatitis, intraductal papillary mucinous tumor (IPMT), and recent onset of diabetes mellitus, particularly if the diabetes occurs during or beyond the sixth decade. In addition inherited syndromes also are associated with an increased risk of pancreatic cancer including familial pancreatic cancer, hereditary pancreatitis, familial adenomatous polyposis syndrome (FAP) and familial atypical multiple mole melanoma (FAMMM) syndrome (hereditary dysplastic nevus syndrome). Of these conditions, recent onset of diabetes may be the best clue and should be included in a clinical profile of patients prior to the onset of symptoms to identify a high-risk group to apply screening strategies for detection of early disease. Contrary to a clinical aphorism that pancreatic cancer patients are elderly, lean and recently may have developed diabetes, we found that patients who develop pancreatic cancer are overweight prior to onset of symptoms compared to controls (body mass index, 28 vs 25). Forty percent had the diagnosis of diabetes made at the time of diagnosis of pancreatic cancer and more patients with a resectable tumor had diabetes (58%) compared to patients with locally unresectable or metastatic disease (37%). Perhaps, screening overweight persons who have new-onset diabetes may lead to a diagnosis of asymptomatic, early, resectable pancreatic cancer.

Key words: CA19-9, diabetes, IAPP (amylin), IPMT, K-ras, pancreatic cancer, pancreatitis, signs, symptoms

Introduction
Pancreatic cancer is a relatively common and deadly tumor. In a community-based population, the age adjusted incidence is 8 and 13 per 100,000 person years in women and men, respectively [1]. It is the fifth and fourth most common tumor in women and men, respectively, and has the lowest 5-year survival of all tumors in the USA [2]. The overall 5-year survival in the USA has increased over the past decade, but is still only 1-3% in whites and 3-5% in blacks [2]. Late diagnosis, resulting in low resection rates (10-20%) [3], is a major reason for poor survival. Patients who undergo resection of the tumor have a 10% chance of surviving 5 years [3]. Five-year survival is related to size of the resected tumor. In our experience, 5-year survival is ~20-30% if the tumor is <2 cm [4], but 5-year survival is nil if the tumor is ≥3 cm [4]. These data give hope that detection of early tumors defined as <2 cm or less may increase 5-year survival appreciably. A major problem is that there is no proven strategy to detect small, early tumors. Furthermore, even if we had such a strategy, we don’t know if it would improve survival.

Symptoms and signs as clues to pancreatic cancer
Nearly a quarter of a century ago we performed a prospective clinical trial of diagnostic tests in patients suspected of having pancreatic cancer on the bases of clinical symptoms and signs [5]. For this study, we selected patients if they were ≥35 years old and had two or more of the following problems for 18 months or less: pain in the upper abdomen; pain extending to the back or night awakening; loss of more than 10% of ideal body weight; obstructive jaundice; or unexplained pancreatitis in patients beyond 50 years of age. All patients had a gold standard diagnosis of symptoms to identify a high-risk group to apply screening strategies for detection of early disease. Of the 70 patients entered into the study, 30 had pancreatic cancer, and of these only 4 had a resectable cancer (13%). These symptoms likely identified patients with advanced disease. For example, more recently, Krech and Walsh reported that 82, 64, 62, 54, and 51% of patients who had unresectable disease had pain, anorexia, early satiety, sleep problems and weight loss, respectively [6]. In addition, back pain predicts unresectability and shortened survival after resection [7]. However, earlier diagnosis might be possible if the onset of symptoms would give rise to suspicion of pancreatic cancer. There is support for this hypothesis because symptoms compatible with upper abdominal disease may be present in 25% of patients up to 6 months prior to diagnosis. Further, 5% of patients may seek medical attention more than 6 months prior to diagnosis [8], but the symptoms may be attributed erroneously to problems such as irritable syndrome [9]. Symptoms, however, may be less common. Grahm and
Andren-Sandberg [10] reported that 27% of 46 consecutive patients with pancreatic cancer had no pain at diagnosis, 53% had little pain, and patients with pancreatic head tumors had less pain compared with patients with body-tail tumors. Also, The clinical profile of patients prior to the onset of symptoms may help to identify a high-risk group to apply screening strategies for detection of early disease.

Pitfalls

Most patients with symptoms highly suggestive and sensitive for pancreatic cancer have other problems to explain their symptoms. In our experience, 57% of patients with these symptoms have other problems [5]. Thirteen percent had non-pancreatic, intraabdominal cancers (lymphomas, small bowel carcinomas, ovarian cancer or uterine cancer) and 44% had non-pancreatic, non-neoplastic disease including negative laparotomy in 23% (irritable syndrome), pancreatitis in 13%, and other miscellaneous problems in 11%.

Early clues

Finding early cancers is uncommon because clues for early cancer have been lacking. Several diseases and inherited syndromes, however, recently have been identified as having an increased risk for developing pancreatic cancer. Diseases include chronic pancreatitis, intraductal papillary mucinous tumor (IPMT), recent onset of diabetes mellitus, particularly if the diabetes occurs during or beyond the sixth decade. Inherited syndromes include familial pancreatic cancer, hereditary pancreatitis, familial adenomatous polyposis syndrome (FAP) and familial atypical multiple mole melanoma (FAMMM) syndrome (hereditary dysplastic nevus syndrome).

The strongest evidence for the development of pancreatic cancer in chronic pancreatitis is in hereditary pancreatitis where the estimated cumulative risk of pancreatic cancer to age 70 is 40% [11]. Diagnosis of pancreatic cancer in hereditary pancreatitis is usually after 35. One of the two specific gene mutations that have been identified for hereditary pancreatitis [12,13] occur in about 60% of patients with the disease. Thus, it is possible to screen families for affected persons and to plan a rational screening program for detecting pancreatic cancer. The cumulative risk for pancreatic cancer in patients with chronic pancreatitis is 2% per decade [14]. The relative risk (ratio of observed to expected cases) ranges from 4 to 16. However, only ~1-2% of pancreatic cancer is due to chronic pancreatitis [14-16].

Intraductal papillary mucinous tumor (IPMT) [17], commonly confused with chronic pancreatitis [18], is characterized by dilatation of the main pancreatic duct or branch ducts associated with mucin overproduction. There may be peripheral lesions consisting of ectatic branch ducts connected to the main duct or cysts that do not connect with the main duct [18], which mimic mucinous cystic neoplasm (MCN). Typical changes evident on CT and ERCP distinguish IPMT from chronic pancreatitis. At ERCP or CT there may be characteristic intraductal filling defects mucus may be seen exuding from the papilla at ERCP [20]. Invasive cancer is present in 25-50% of surgical specimens [18,20], but even if invasive cancer is not present the lesion is premalignant, and benign lesions contain several genetic mutations associated with pancreatic cancer [19,21].

Diabetes mellitus may herald pancreatic cancer, particularly if the diagnosis of diabetes is made during or beyond the sixth decade and there is no family history of diabetes [22]. Diabetes is present in 60 [23] to 81% [24] of patients with pancreatic cancer and most patients are diagnosed within 2 years of recognizing pancreatic cancer. In a recent study [23], 56% had diabetes diagnosed concomitantly with the tumor and 16% had the diagnosis of diabetes made 2 years prior to the diagnosis of the cancer. With a meta-analysis, the risk of developing pancreatic cancer in patients with diabetes of more than 1 year's duration was 2.1 (95% CI: 1.6-2.8) [25]. Sixty-six percent of patients with pancreatic cancer and diabetes have no family history of diabetes [22].

Some pancreatic cancers are inherited. Seven to 8% of patients with pancreatic cancer have a family history of pancreatic cancer, which is an ~13-fold increase compared to 0.6% of controls [26,27]. In a recent prospective survey of our pancreatic cancer patients attending a pancreatic clinic, 10% of them had one or more first degree relatives who died of pancreatic cancer [28]. In familial adenomatous polyposis syndrome (FAP), there is 4.46 relative risk (95% CI: 1.2-11.4) for developing pancreatic cancer in polyposis patients and in family members at risk, but the absolute risk is low—21/100,000 person years [29]. Pancreatic cancer risk is increased in familial atypical multiple mole melanoma (FAMMM) syndrome (hereditary dysplastic nevus syndrome) [30] but only in some kindreds [31]. In this disorder, a gene on chromosome 9p, p16INK4 has been implicated in the pathogenesis of the melanoma. However, risk of pancreatic cancer (13-fold) is only in kindreds with an impaired function of the p16INK4 protein (p16M alleles); without impaired function of p16INK4 protein (p16W alleles), there is no increased risk for pancreatic cancer.

Many environmental factors are associated with an increased risk for pancreatic cancer but they are so ubiquitous that it is impossible to use them as clues for diagnosis. The interpretation of most data suggests that environmental risks associated with pancreatic cancer may be related to exposure to aromatic amines. For example the most prominent risk factor is cigarette smoking, and about 30 aromatic amines are in cigarette smoke [32]. Similarly, carcinogenic and mutagenic heterocyclic aromatic amines present in cooked meat and fish (formed during cooking as pyrolysis products of amino acids and proteins) [33-35] may be the basis for the association between meat and fish consumption and risk of pancreatic cancer [36-38]. Occupations (chemists, petrochemical workers, hairdressers and rubber workers) with an increased exposure to aromatic amines have a greater risk of pancreatic cancer [39,40]. Conversely, some plant components (dithiolthiones and limonene) may induce glutathione transferase and increase activation of heterocyclic amines [41,42], and explain why eating fruits and vegetables may protect against development of pancreatic cancer.

The clinical profile of patients prior to the onset of symptoms may help to identify a high-risk group to apply screening strategies for detection of early disease. A clinical
aphorism is that pancreatic cancer patients are elderly, lean and recently may have developed diabetes. Contrary to this aphorism, in an ongoing study [43] we found that patients who develop pancreatic cancer are overweight prior to onset of symptoms compared to controls (body mass index, 28 vs 25). Forty percent had the diagnosis of diabetes made at the time of diagnosis of pancreatic cancer and more patients with a resectable tumor had diabetes (58%) compared to patients with locally unresectable or metastatic disease (37%). Perhaps, screening overweight persons who have new-onset diabetes may lead to a diagnosis of asymptomatic, early, and resectable pancreatic cancer.

Ideally, all patients at risk for pancreatic cancer should be investigated and followed closely for development of pancreatic cancer. However, it is unknown when to begin screening and current tumor markers are too insensitive and to detect early pancreatic cancer. However, combination of tumor markers may increase sensitivity for detection of small tumors. Recent studies in our unit have demonstrated that IAPP (amylin) in blood and K-ras measured in DNA extracted from pancreatic secretions obtained at endoscopy are approximately 50% sensitive for detection of pancreatic cancer, but in comparison to CA 19-9 sensitivity is independent of stage of tumor [44]. Thus, a battery of markers may increase sensitivity for detecting small tumors, particularly in patients who are obese and have recent onset of diabetes [43].

Currently, specific recommendations cannot be given. It seems prudent, however, to initiate screening 10 years before the age that pancreatic cancer was first diagnosed in familial pancreatic cancer and in the various syndromes, and at age 35 in hereditary pancreatitis. Spiral CT and EUS have the best sensitivity for detecting pancreatic cancer, and are the imaging tests that should be considered for screening. However, the differentiation between inflammatory and neoplastic masses with imaging tests is problematic. This topic, however, is beyond the scope of this review.

References