Review
Future Oncology

Limitations in improving detection of pancreatic adenocarcinoma

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Objective: To review the current trends in pancreatic cancer research and propose alternatives for an earlier diagnosis. **Method:** A search was conducted using the PubMed and Scielo electronic databases to find out statistics related to the incidence of pancreatic cancer. **Results:** Pancreatic cancer is the fourth most common cause of cancer mortality in the USA; in Colombia the incidence of this neoplasia is 4.5 per 100,000 individuals; and in Peru, amongst digestive diseases, it is the fifth most common cause. In Brazil and Chile this cancer has increased in incidence, while in Mexico, it has decreased in terms of the relative percentage of gastrointestinal cancers from 1976 to 2003. Chronic pancreatitis, cigarette smoking, diabetes, obesity and dietary mutagen exposure are the most consistent risk factors implicated in the development of pancreatic cancer; however, the genetic and molecular changes underlying the epidemiological association between these factors and pancreatic cancer remain largely unknown, and only 5–10% are hereditary in nature. **Conclusion:** The prognosis for pancreatic cancer has not changed substantially for at least the last 20 years. The most useful tumor marker for pancreatic adenocarcinoma is still the carbohydrate antigen 19–9 (CA19–9). Currently, a multimodal-screening approach of endoscopic ultrasound, computed tomography and endoscopic retrograde cholangiopancreatography are the most effective methods to detect pancreatic cancer in high-risk patients. Future options for early detection of this malignancy are focused on new molecular markers, telomerase enzyme, receptor-targeted imaging using multifunctional nanoparticles, detection of glycan changes and epigenetics.

Pancreatic cancer is the fourth most common cause of cancer mortality in the USA and its incidence is estimated to be around nine patients per 100,000 individuals [1]. Information on this malignancy in Latin America is scarce; in Brazil analyses have demonstrated a 10.23% increase in the mortality rate [2]. Among Chilean women there has been also a significant increase in this neoplasm [3], and while the incidence in Colombia is 4.5 per 100,000 individuals [4], in Mexico pancreatic cancer has had a slight decrease in the relative percentage occurence of gastrointestinal cancers from 1976 to 2003 [5]. In Peru, amongst digestive diseases, pancreatic cancer is the fifth most common [6].

For all stages combined, the 1-year survival rate for pancreatic cancer is approximately 20%, and the overall 5-year survival rate has remained dismally poor, at less than 5% [1]. Complete surgical resection remains the only curative treatment for pancreatic cancer, but because of the typically late onset of symptoms, only approximately 15–20% of cases are amenable to surgical resection at the time of diagnosis. Of the remaining 80–85% of patients, 40% present with advanced locoregional disease precluding complete resection, with a median survival time (MST) of 6–11 months, and the other 45% of patients present with metastatic disease, with a MST of 3–6 months [7,8].

The only possibility of cure, albeit small, is based on the combination of complete resection with negative histopathological margins (R0 resection) with adjuvant treatment [9].

At present, the most effective screening method for pancreatic cancer in high-risk patients is a multimodal screening approach of endoscopic ultrasound (EUS), computed tomography (CT) and endoscopic retrograde cholangiopancreatography (ERCP). Continued efforts are therefore needed to elucidate effective testing to identify patients with nonhereditary risk factors who will benefit from screening protocols. A combined approach of serum markers, genetic markers and specific imaging studies may prove to be the future of pancreatic screening [10].

Risk factors

The median age at diagnosis for pancreatic cancer is 69 years in white people and 65 years in

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black people, with a male:female ratio of 1.2–1.5:1. Risk factors are not well understood, since most cases seem to develop sporadically. Chronic pancreatitis [11], cigarette smoking [12,13], diabetes [14], obesity [15] and dietary mutagen exposure [16] have been implicated; however, the genetic and molecular changes underlying the epidemiological association between these factors and pancreatic cancer remain largely unknown and only 5–10% are hereditary in nature. Furthermore, research on the molecular pathology of pancreatic adenocarcinoma is particularly difficult due to limited accessibility to the organ for biopsy. Morphological observations suggest that pancreatic intraductal hyperproliferation, especially atypical papillary duct lesions, are the precursors of invasive ductal cancer [17].

Clinical setting

The most common signs and symptoms of pancreatic adenocarcinoma are abdominal pain, jaundice, indigestion, nausea, vomiting, weakness, exacerbation of diabetes, backache, weight loss, dizziness and diarrhea – all of these depending on the stage [18]. Migratory thrombophlebitis (Trousseau sign) may also be a sign of the malignancy [101]. Patients with jaundice may have a palpable gallbladder (Courvoisier sign) and skin excoriations from pruritus. Patients presenting with end-stage disease may have ascites, a palpable abdominal mass, hepatomegaly from liver metastases or splenomegaly from portal vein obstruction. Disappointingly, up to 17.3% of patients have no symptoms until an advanced stage is reached [101].

Laboratory findings

The laboratory findings in patients with pancreatic cancer are usually nonspecific. As with many chronic diseases, a mild normochromic anemia may be present [19]. Thrombocytosis is also sometimes observed. Patients presenting an obstructive jaundice show significant elevations in bilirubin, alkaline phosphatase, γ-glutamyl transpeptidase and, to a lesser extent, aspartate aminotransferase and alanine aminotransferase. Amylase and lipase are infrequently elevated, unless the patient presents an acute pancreatitis secondary to the pancreatic cancer.

Liver metastases on their own do not usually cause jaundice and usually result in relatively low-grade elevations of alkaline phosphatase and transaminase levels. Patients may also have laboratory evidence of malnutrition, such as low levels of serum albumin and cholesterol [20].

Various new tumor markers, including SPan-1, DUPAN-2, and carbohydrate antigen 50 (CA 50), have proven to offer new hope for improved diagnosis of pancreatic cancer [21]. The most useful tumor marker for pancreatic adenocarcinoma is still CA 19–9 [22], a murine monoclonal antibody originally created against colorectal cancer cells. The reference range of CA 19-9 is less than 33–37 U/ml. A total of 75–85% of patients with pancreatic cancer have elevated CA 19-9 levels. In the absence of biliary obstruction or benign pancreatic disease, a CA 19-9 value greater than 100 U/ml is highly specific for malignancy, usually pancreatic. Evaluation of CA 19-9 levels has been used as an adjunct to imaging studies to help determine the resectability potential of pancreatic cancer. Less than 4% of patients with a CA 19-9 level of more than 300 U/ml have been found to have resectable tumors. Unfortunately, CA 19-9 is less sensitive for small early-stage pancreatic cancer, and thus it has not proven to be effective for early detection or as a screening tool. An elevated CA 19-9 level is found in 0.2% of an asymptomatic population older than 40 years of age. Of these elevations, 80% are false-positive results. If only symptomatic patients are studied, 4.3% have elevated CA 19-9 levels. Two-thirds of these results are false-positive. To date, no standardized role has been found for CA 19-9 measurements in early detection of pancreatic cancer, and the usefulness of this practice must still be classified as a supplement to other diagnostic modalities.

Carcinoembryonic antigen (CEA) is a high molecular weight glycoprotein normally found in fetal tissues. It has been commonly used as a tumor marker in other gastrointestinal malignancies. Other multiple benign and malignant conditions can lead to elevated CEA levels; therefore, CEA is neither a sensitive nor specific marker for pancreatic cancer. Notwithstanding, there are contradictory opinions related to its usefulness [23]. The initial tumor marker CA 50 value can help indicate in which patients a pancreatic malignancy should be suspected [24].

Image studies

Transcutaneous ultrasonography (TUS) is still considered useful for the initial screening of pancreatic cancer [25], especially in evaluating patients who present possible obstructive jaundice. TUS is less useful in pancreatic cancer than CT scanning because the pancreas is often obscured by overlying gas. Additionally, the depth of the pancreas from the abdominal wall limits transcutaneous ultrasonic imaging to

a lower frequency (2–5 MHz); hence, a lower-resolution ultrasonographic image is obtained. Therefore, TUS can help detect 60–70% of pancreatic carcinomas, yet more than 40% of the lesions smaller than 3 cm are overlooked [101], and for staging other imaging techniques must be employed.

There is a new and promising application of contrast-enhanced ultrasonography (CEUS) to the study of the pancreas. The perfusion of the pancreas is well correlated to the semeiology of the gland parenchymography at CEUS. This technique can be used to better identify pancreatic lesions with respect to conventional ultrasound, or to characterize pancreatic lesions already visible with ultrasonography. Moreover, CEUS by the Agent Detection Imaging (ADI) technique is also useful for the diagnosis of pancreatic tumors [26]. The staging of some pancreatic lesions can be improved by the use of contrast media [27].

Computed tomography

Due to its ubiquitous availability and ability to image the whole abdomen and pelvis, abdominal CT scanning is usually the mainstay of initial diagnostic modalities used for assessing patients suspected to have pancreatic cancer [28]. Scanners can detect 70–80% of pancreatic cancers. Unfortunately, similar to TUS, 40–50% of tumors smaller than 3 cm are missed, and these are the tumors most likely to be resectable. Newer models using multidetector row computed tomography (MDCT) and dual-phase contrast enhancement have significantly improved the sensitivity and specificity of abdominal CT findings in patients with pancreatic cancer [29]. MDCT, in particular, is ideally suited for detecting pancreatic tumors because of the high spatial resolution with a detection rate between 70 and 100%, and a sensitivity of 94% and a specificity of 89% for resectability. MDCT is also an ideal tool for the detection of intraductal papillary mucinous neoplasms (IPMN) [30].

Dual-phase spiral CT findings are approximately 80% accurate to help determine the resectability potential of pancreatic cancer, and this is especially good at assessing major arterial involvement [31,32]. Furthermore, CT scanning can be used to direct fine-needle aspiration of pancreatic masses. However, small tumors can still be omitted, even with the most advanced CT scanning currently available.

Magnetic resonance imaging

Diagnosis of adenocarcinoma by magnetic resonance imaging (MRI) is best with fat-suppression and 'fast' imaging techniques – tumors most often appear as a region of decreased signal within the pancreas [33] – but it does not appear to be superior to spiral CT scanning [34].

Because of the difficulty of working within intense magnetic fields, MRI is limited by the inability to perform MRI-directed needle aspirations; however, technical advances including ultra-high-field magnetic resonance at 3.0 T, parallel imaging techniques and multichannel receive coils of the abdomen have promoted MRI of the pancreas [35]. Specifically, in patients with jaundice, magnetic resonance cholangiopancreatography (MRCP) is now established as a robust noninvasive tool for the evaluation of biliary and pancreatic pathology [36].

Endoscopic ultrasonography

Endoscopic ultrasonography obviates the physical limitations of TUS by placing a high-frequency ultrasonographic transducer on an endoscope, which is then positioned in the stomach or duodenum endoscopically to help visualize the head, body and tail of the pancreas. Additionally, because of the proximity of the pancreas to the EUS transducer, high-frequency ultrasonography can be used to produce very high-resolution images [37]. Where expert EUS is available, it has proven to be the most sensitive and specific diagnostic test for pancreatic cancer. In numerous series, EUS has detection rates of 95–100% for all the pancreatic cancers [8], including those under 3 cm. EUS is as accurate as ERCP or MRCP for assessing the etiology of obstructive jaundice. An additional significant diagnostic advantage is EUS-guided fine-needle aspiration, which allows for the simultaneous cytologic confirmation of pancreatic cancer at the time of EUS diagnosis [8]. In fact, EUS should be seriously considered as the next step in the evaluation of patients with focal enlargement of the pancreas when clinical suspicion of malignancy exists [38].

EUS appears to be equivalent to dual-phase spiral CT scanning for assessing tumor resectability potential and appears to better assess involvement of the portal vein/superior mesenteric vein. EUS is better than CT scanning in helping to detect abnormal lymph nodes around the pancreas and celiac axis [39].

Endoscopic retrograde cholangiopancreatography

Endoscopic retrograde cholangiopancreatography is important in the diagnosis of ampullary

tumors by direct visualization and biopsy. All other pancreatic tumors are detectable only if they impinge on the pancreatic duct, meaning that small early cancers and those situated in the uncinate process can be missed by this technique. ERCP is often performed first to relieve obstruction biliary stenting [40], and to provide relief of jaundice and the associated symptom of pruritus [41]. The prediction model with ERCP at a tertiary referral hospital determined a 67% probability of detecting pancreatic cancer [42]. This technique carries a 5–10% risk of significant complications of the procedure [43,44].

Positron emission tomography scanning

Positron emission tomography (PET) scanning uses 18F-fluorodeoxyglucose (18F-FDG) to image both the primary tumor and metastatic disease. PET is complementary to abdominal CT and allows the detection of unsuspected distant metastases [40]. Furthermore, 18F-FDG PET-CT achieves a comparably high diagnostic impact when evaluating small solid pancreatic lesions versus conventional reference imaging modalities, and additional clinical diagnoses are derived from concomitant whole-body PET-CT imaging [45].

Needle aspiration

The necessity of obtaining a cytologic or tissue diagnosis of pancreatic cancer prior to operating remains controversial [46]. Nonoperative techniques to establish histological diagnosis are percutaneous fine-needle aspiration or biopsy, intraductal aspiration of fluids for cytology and intraductal collection methods including brush cytology, fine-needle aspiration, forceps biopsy, and stent retrieval with cytology examination [47,48].

EUS-guided fine-needle aspiration has proven to be the most effective means for making a definitive cytologic diagnosis of pancreatic cancer [49]. Using EUS-guided fine-needle aspirations, a cytologic diagnosis can be made in up to 70% of patients and provides the additional advantage of aspiration through tissue that would ultimately be included in the operative field should the patient undergo resection [50]. Also, this technique can avoid the risk of peritoneal tumor spread. Thus, for potentially resectable tumors, EUS-guided fine-needle aspiration is the preferred biopsy technique if it is available and if a biopsy needs to be obtained. On the other hand, the sensitivity, specificity, positive and negative predictive values and diagnostic efficiency of percutaneous CT-guided fine-needle aspiration cytology in detecting malignancy are 91, 100, 100, 73, and 93%, respectively [51].

Staging laparoscopy or laparotomy

Selective use of diagnostic laparoscopy staging is potentially helpful in determination of resectability. Laparotomy remains the definitive method for determining the resectability of pancreatic cancer, with or without portal vein resection, and should be undertaken in suitable patients without clear-cut evidence of irresectability [52].

Histology

WHO establishes the classification of pancreatic tumors (**Box 1**). Overall, 75% of pancreatic tumors appear in the head of the pancreas. Among these, the majority (95%) correspond to the exocrine portion. On the other hand, several histological variants, each one with distinct clinical features, prognosis and pathogenesis, have been described, ductal adenocarcinoma being the most common and lethal subtype.

Of all the pancreatic cancers, 80% are adenocarcinomas of the ductal epithelium (**Figure 1**). Only 2% of tumors of the exocrine pancreas are benign. The ductal adenocarcinomas are firm and poorly defined masses of 1.5–5 cm. Usually, pancreatic cancers metastasize first to regional lymph nodes and then to the liver and less commonly, to the lungs. These can also directly invade the surrounding visceral organs such as the duodenum, stomach and colon [101].

- Based on light-microscopy, three noninvasive precursor lesions of pancreatic cancer have been described [53]: IPMN, mucinous cystic neoplasms and pancreatic intraepithelial neoplasia (PanIN) [54]. In recent years, IPMN have gained recognition as premalignant precursors to pancreatic cancer that enable early detection and are often found incidentally at imaging [55]. PanIN is, in turn, divided into three different grades based on the epithelial cytology and architectural atypia [56]:
- PanIN-1: lesions with only minimal atypia, these are subdivided into flat (PanIN-1A) and papillary types (PanIN-1B);
- PanIN-2: moderate atypia;
- PanIN-3: marked atypia.

Papillary adenocarcinoma and the well-differentiated type of tubular adenocarcinoma are more frequent in TS1 pancreatic cancer than the larger tumors, suggesting that further genetic and phenotypic changes occur during their

progression [101]. Unfortunately, small pancreatic cancer does not necessarily mean early pancreatic cancer, and surgery alone is not sufficient to cure this disease.

The infiltrating ductal adenocarcinoma is characterized by glandular structures that can be well, moderately or poorly differentiated. All of these are embedded in desmoplastic stroma, which accounts for their firm consistency. Vascular and perineural invasions are present in the majority of cases.

Less common histologic appearances of exocrine pancreatic cancers include giant cell carcinoma, adenosquamous carcinoma, microglandular adenocarcinoma, mucinous carcinoma, cystadenocarcinoma, papillary cystic carcinoma, acinar cystadenocarcinoma and acinar cell cystadenocarcinoma.

Although there are no histochemical or immunohistochemical markers that unequivocally distinguish pancreatic from extrapancreatic adenocarcinoma, the majority of pancreatic cancers express cytokeratins 7, 8, 13, 18 and 19, CA19–9, B72–3, CA125 and DUPAN, as well as mucins MUC1, MUC3, MUC4 and MUC5 [57].

Box 1. WHO histological classification of exocrine pancreatic tumors.

Epithelial tumors

Benign

- Serous cystadenoma
- Mucinous cystadenoma
- Intraductal papillary-mucinous adenoma
- Mature teratoma

Borderline (uncertain malignant potential)

- Mucinous cystic neoplasm with moderate dysplasia
- Intraductal papillary-mucinous neoplasm with moderate dysplasia
- Solid-pseudopapillary neoplasm

- Malignant
- Ductal adenocarcinoma
- Mucinous noncystic carcinoma
- Signet ring cell carcinoma
- Adenosquamous carcinoma
- Undifferentiated (anaplastic) carcinoma
- Undifferentiated carcinoma with osteoclast-like giant cells
- Mixed ductal-endocrine carcinoma
- Serous cystadenocarcinoma
- Mucinous cystadenocarcinoma
  - Noninvasive
  - Invasive
- Intraductal papillary–mucinous carcinoma
  - Noninvasive
  - Invasive (papillary–mucinous carcinoma)
- Acinar cell carcinoma
- Acinar cell cystadenocarcinoma
- Mixed acinar–endocrine carcinoma
- Pancreatoblastoma
- Solid-pseudopapillary carcinoma
- Others

Nonepithelial tumors

Secondary tumors

Molecular studies

Pancreatic cancers contain an average of 63 genetic alterations, the majority of which are point mutations. These alterations define a core set of 12 cellular signaling pathways and processes that are each genetically altered in 67–100% of the tumors. Dysregulation of these core pathways and processes through mutation can explain the major features of pancreatic tumorigenesis [58]. Epigenetic modifications are important events in regulation of gene expression and cancer progression. Knowledge regarding the methylation of cytosine residues in CpG dinucleotides of pancreatic cancer-specific genes could support the development of earlier diagnostic assays and new treatment strategies. In addition, therapeutic approaches are proposed by two recent patents utilizing modulators of DNA cytosine-5 methyltransferase, such as decitabine or C-5 methylcytosine. Additionally, a patent introduces a method that couples an early cancer-related and tissue- or cell-specific gene marker detection assay, useful as a simultaneous screening test for cancers, including pancreatic cancer [59].

Many genes undergo aberrant methylation in human cancers, and microarray platforms enable more comprehensive profiling of aberrant DNA methylation patterns. Promoter and CpG island array analysis finds aberrant methylation of hundreds of promoters and CpG islands in pancreatic cancer cells [60].

Molecular pathology of primitive lesions that lead to invasive pancreatic adenocarcinoma is the key to our understanding of the mechanisms underlying the development of this cancer, and will probably help us in earlier diagnosis and better therapeutic results [54]. Although over 400 molecular genetic defects have been associated with pancreatic cancer, it is unclear which marker is associated with early tumorigenesis and furthermore, the difficulty in obtaining samples from the pancreas limits the utility of such methods in the research setting. The results of two studies show that 100% of pancreatic adenocarcinomas have a mutation that affects at least one gene involved in the TGF-β pathway [61,62].

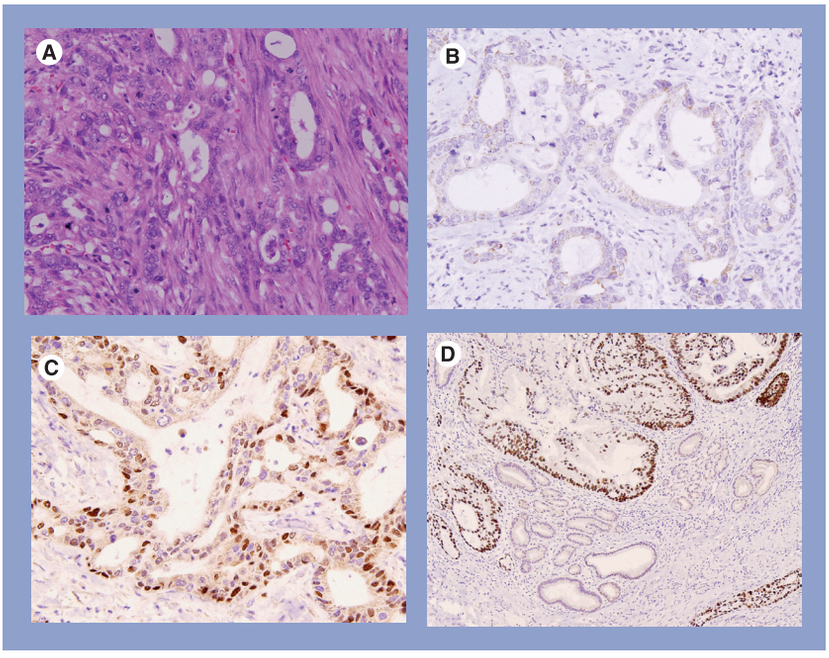

Figure 1. Ductal adenocarcinoma of the pancreas. (A) Moderately/poorly differentiated: note the mixture of medium-sized tubular structures of variable shape and nest with frequent mitotic figures, embedded in desmoplastic stroma (hematoxylin eosin stain, 40×). **(B–D)** Representative photomicrographs illustrating some immunohistochemical abnormalities in infiltrating pancreatic cancer: absence of nuclear p16 labeling **(B)** with diffuse nuclear labeling of cyclin D1 **(C)** and p53 **(D)**. In **(D)**, note the absence of this protein labeling in the normal pancreatic ducts.

Recent studies have shown that in human pancreatic cancer, a specific sequence of oncogene and tumor suppressor gene alterations are observed, just as in colon cancer. Based on the extensive molecular analysis, a multistep progression model, in which specific alterations occur at specific stages of the malignancy, has been proposed. The evidence suggests that some molecular abnormalities are associated with morphology patterns from PanIN to the invasive adenocarcinoma as follows [63]:

- Early changes: upregulation of *p21 WAF1/CIP1*, telomere shortening and *K-ras* point mutation. The latter occurs in approximately 90% of pancreatic cancers [64], resulting in a protein that is constitutively active to signaling the growth and differentiation programs via protein kinase receptors [65]. Moreover, the high frequency of RAS mutations in PanIN suggests a key role as an initiating event for pancreatic cancer formation.
- Intermediate changes: upregulation of cyclin D1 leads to a constitutive phosphorylation of pRb and deregulated E2F activity, altering in such a way the fine-tuning control of the G1/S-phase transition of the cell cycle. Alterations in this pathway, specifically nuclear overexpression of cyclin D1, has been demonstrated in around 60–85% of invasive pancreatic adenocarcinomas [63]. On the other hand, dysregulation of the tumor suppressor *p16INK4* has been found in over 27–95%, including changes such as inactivated homozygous deletions, intragenic mutations or methylation at the level of promoter region [66].
- Late changes: mutations of *p53* are also present in approximately 50–75% of pancreatic cancer, most frequently involving intragenic mutations combined with loss of the second allele [57]. Other molecular alterations include *BRCA2* and *DPC4/SMAD4*, a mediator of *TGF*-β antiproliferative signals. The inactivation of *TGF*-β signaling pathway provides not only a selective growth advantage, but also modulates angiogenesis, as well as the expression of genes implicated with cell adhesion and invasion. Importantly, it has been shown that infiltrating pancreatic cancers have accumulated these genetic alterations by the time they are clinically present (Figure 1).

Potential specimen sources for analysis include serum or plasma, pancreatic juice and pancreatic cells obtained by fine-needle aspiration or cytological brushings. Suggested markers to be evaluated are K-ras, p53, p16, DPC4, macrophage inhibitory cytokine-1 (MIC-1), osteopontin and tissue inhibitor of metalloproteinase 1, amongst others [57].

More biological markers are needed for the early detection of pancreatic cancer. Telomerase activation in response to telomere crisis, followed by telomere shortening, is thought to be a crucial event in the development of most human cancers. It has been published that the average telomere length decreases with IPMN progression. Upregulated human telomerase reverse transcriptase expression is detectable and increases gradually with cancer development, and is primarily observed at the borderline IPMN stage and then in more advanced histopathologies. Progressive telomere shortening predominantly occurs during early IPMN carcinogenesis before telomerase activation and progression from borderline to carcinoma *in situ* [67]. Interestingly, telomerase activity is detected in pancreatic cancer, but not in normal pancreas [68]; thus, it has been postulated that cytology and telomerase activity in cells obtained by pancreatic duct brushing may complement each other for the diagnosis of pancreatic cancer [69]. It is important to mention

that in order to detect telomerase activity, the protein must be extracted from viable cancer cells. In stool samples, such viable cells seem to be too rare.

A new potential molecular imaging agent for the detection of pancreatic cancer is based on targeting urokinase plasminogen activator receptor (uPAR), a cellular receptor that is highly expressed in pancreatic cancer and tumor stromal cells, using biodegradable multifunctional nanoparticles [70]. A novel labeling method is based on gold nanoparticles stabilized by heterobifunctional polyethylene glycol (PEG), which could provide a facile identification of cancer tissue by optical detection [71].

The detection of glycan changes, associated with subsets of glycoforms in serum glycoproteins that are specific to the tumor location, could be the basis for developing more specific biomarkers [72].

Staging

Only 20% of all patients presenting pancreatic cancer are ultimately found to have easily resectable tumors with no evidence of local advancement. No survival benefit is achieved for patients undergoing noncurative resections for pancreatic cancer. Thus, to avoid operating on patients who cannot benefit from the operation, accurate preoperative staging is very important.

Cancer of the exocrine pancreas is classified by the tumor, nodal, metastases (TNM) staging system that has recently been modified by the American Joint Committee on Cancer (**Box 2**). Unfortunately, at initial presentation, only 20% of patients present with stage I disease, 40% present with locally advanced disease and 40% present with disease metastatic to nodes or distant sites.

Treatment

The classical Whipple's partial pancreatoduodenectomy (PPD) operation is still the standard procedure for cancer of the head of the pancreas, but despite recent improvements in operative techniques and perioperative management, this type of surgery is associated with a relatively high rate of postoperative complications [73]. During the last two decades, pylorus-preserving pancreatoduodenectomy (PD) has been evolved as a more conservative procedure in order to omit the consequences of partial gastrectomy [74]. Another option is PD with lymphadenectomy, including vascular resection.

For patients with small or low-grade malignant neoplasms, as well as small pancreatic metastases located in the mid-portion of the pancreas, central pancreatectomy (CP) is emerging as a safe and effective option with a low risk of developing *de novo* exocrine and/or endocrine insufficiency. Pyloric preservation can frequently be performed at the time of PD, although some reports have linked it to inferior outcomes such as delayed gastric emptying [75]. Due to the development of modern instruments, laparoscopic operations have become more successful, even in malignant pancreatic diseases [76].

The indication of total pancreatectomy (TP) is limited to locally extended tumors that cannot be removed by PD or distal pancreatectomy with tumor-free surgical margins. Consequently, TP has not been adopted as a routine procedure by most surgeons. On the other hand, a more complex treatment with surgery and chemotherapy is required in case of advanced distal pancreatic tumors, provided that safe and experienced surgery is available.

Adenocarcinoma of the pancreas presents a number of therapeutic challenges. Given the poor long-term outcomes after PD, many surgeons have sought to improve survival via a radical or 'extended' pancreatectomy that may

Box 2. American Joint Committee on Cancer classification of pancreatic cancer.

Tumor
- TX – Primary tumor cannot be assessed
- T0 – No evidence of primary tumor
- Tis – Carcinoma *in situ*
- T1 – Tumor limited to the pancreas, 2 cm or smaller in greatest dimension
- T2 – Tumor limited to the pancreas, larger than 2 cm in greatest dimension
- T3 – Tumor extension beyond the pancreas (e.g., duodenum, bile duct, portal or superior mesenteric vein) but not involving the celiac axis or superior mesenteric artery
- T4 – Tumor involves the celiac axis or superior mesenteric arteries

Regional lymph nodes
- NX – Regional lymph nodes cannot be assessed
- N0 – No regional lymph node metastasis
- N1 – Regional lymph node metastasis

Distant metastasis
- MX – Distant metastasis cannot be assessed
- M0 – No distant metastasis
- M1 – Distant metastasis

Stage grouping
- Stage 0 – Tis, N0, M0
- Stage IA – T1, N0, M0
- Stage IB – T2, N0, M0
- Stage IIA – T3, N0, M0
- Stage IIB – T1-3, N1, M0
- Stage III – T4, Any N, M0
- Stage IV – Any T, Any N, M1

M: Distant metastasis; N: Regional lymph nodes; T: Tumor.

include: TP, extended lymph node dissection, and portal/mesenteric vascular resections [77].

Gemcitabine, a deoxycytidine nucleoside analog, is the current standard chemotherapy used as first-line treatment for patients with locally advanced or metastatic cancer of the pancreas, and extends life survival by 5.7 months. Troxacitabine (Troxatyl™) is the first unnatural L-nucleoside analog to show potent preclinical antitumor activity and is currently under clinical research [78].

Inhibition of EGF receptor (EGFR) by monoclonal antibodies that inhibit ligand binding or by tyrosine kinase inhibitors (TKIs) that bind to the ATP binding site of the growth factor receptor represents another therapeutic approach for pancreatic adenocarcinoma. Cetuximab (Erbitux®) is the first human–mouse chimeric IgG1 antibody that has been approved for EGFR-positive colorectal cancer. Currently, it is used in large clinical trials for EGFR-positive expression in pancreatic cancer. This novel agent presents more than one mechanism of action, including arrest of cell cycle, activation of apoptosis, inhibition of angiogenesis and inhibition of distant metastasis. It is interesting that EGFR inhibition contributes to angiogenic inhibition [79]. The next step is a clinical study comparing gemcitabine alone and in combination with an EGFR inhibitor. Another novel agent that could be used as targeted therapy in pancreatic cancer is ABX-EGF, a fully humanized IgG2 monoclonal antibody that has a higher binding affinity to EGFR than cetuximab.

Several TKIs (PKC-412, erlotinib) have been tried as targeted therapies in pancreatic adenocarcinoma [80,81]. The addition of erlotinib to gemcitabine has been shown to prolong survival of patients treated for advanced pancreatic cancer in the National Cancer Institute of Canada PA.3 trial [82]. The most frequent toxicities associated with the addition of erlotinib are diarrhea and rash – the latter one appearing to be predictive of outcome. Also, the combination of cetuximab and erlotinib increases the efficacy of gemcitabine-radiation [83].

Another therapeutic approach is antisense therapy. The mechanism of action is the inhibition of protein expression through trapping mRNA by specific RNA sequences. There are ongoing trials on murine xenografts into the human pancreatic cancer cell line, AsPC-1 [84]. Unfortunately, advanced pancreatic cancer thus remains a highly unmet medical need, and new therapeutic agents are required for this population of patients.

Prognosis

Despite scientific efforts and significant progress in knowledge regarding the basic cellular events in pancreatic cancer, survival rates have not changed significantly during the last 20 years. Tonini *et al.* [85] have established that the markers with the strongest evidence as independent predictors of patient outcome include, p16, MMP7 and VEGF, but, novel diagnostic strategies are needed in order to improve the prognosis of patients with pancreatic cancer.

Whom to study

The ideal study population would consist principally of people above 45 years of age showing obesity, diabetes, history of smoking, previous pancreatitis and family background [86,87]. Clearly, it would be impractical to screen all patients with only one of these factors; even if a definite risk factor was identified, it is unclear whether screening would be beneficial because a precursor lesion to pancreatic cancer cannot be easily identified. In this regard, screening for a mass lesion is suboptimal since most patients, including those with very small tumors, die from the disease.

Serum CEA and CA 19-9 levels were unhelpful in diagnosing dysplasia. Likewise, several studies have shown *K-ras* oncogene mutational analysis to be more sensitive than conventional cytology, but subject to false-positive results in patients with pancreatitis [88].

The ERCP and EUS findings appear to be somewhat nonspecific and overly similar to chronic pancreatitis to be used to diagnose dysplasia in the general population. Clearly, further studies are urgently needed to determine risk factors for pancreatic cancer and more specific methods to identify precancerous lesions of the pancreas.

It has been statistically observed that 5–10% of patients with pancreatic cancer have a close relative with the same cancer, whereas this rate among controls is only approximately 0.6% [89]. The risk of a person developing pancreatic cancer is increased when there is a familial history of any cancer amongst first-degree relatives [90]. Therefore, biological and molecular staging of this disease may lead us to earlier diagnoses, efficient familial counseling, better management and new therapeutic approaches.

Prevention

At the present time, the best advice to reduce the risk of pancreatic cancer is to avoid tobacco smoking, maintain a healthy weight, be physically active and eat five or more portions of fruit and

vegetables a day [91].

As obesity is associated with pancreatic cancer and is increasing dramatically in developing countries, we believe that clinicians might find cases of this malignancy in patients at younger ages than they did a few years ago.

Final recommendation

Among developing countries, the highest rates of pancreatic adenocarcinoma are observed in Central and South America [92]. This increasing mortality trend (Figure 2) must prompt a review of the quality of the data registration, the existing health programs, and design of new strategies that will lead us to improve prevention, access and quality of treatment, and finally to decrease cancer mortality. New strategies, such as incorporating molecular medicine departments in public hospitals, must be called on to change the current outcome.

A step in the right direction to reduce pancreatic cancer mortality should be the design of a telomerase detector chip for stools, a common screening test for gastrointestinal neoplasias above 40 years of age and, in case of positivity, taking the next steps to specify the origin of the malignancy.

Conclusion

Pancreatic cancer is still a devastating disease with a poor prognosis that has not changed substantially at least for the last 20 years. Chronic pancreatitis [11], cigarette smoking [12,13], diabetes [14], obesity [15] and dietary mutagen exposure [16] are considered as the principal risk factors for development of this neoplasia.

Thus far, the most useful tumor marker for pancreatic adenocarcinoma is still the CA19–9 [22], but new tumor markers have been shown to offer new hope to improve the diagnosis of pancreatic cancer [21].

PPD including vascular resection still presents the optimal treatment for carcinomas in the head of pancreas. On the other hand, gemcitabine plus erlotinib is the current standard chemotherapy used as first-line treatment for patients with locally advanced or metastatic cancer of the pancreas.

It is mandatory to design new alternatives using advanced molecular tools to reach early detection of pancreatic cancer, because only approximately 15–20% of cases are amenable to surgical resection at the time of diagnosis.

Future perspective

As the world population is becoming older, the epidemiological data will show an increase in the incidence of pancreatic cancer in the next 10 years. Unfortunately therapeutic options are very limited because of late diagnosis, stressing the importance of the assessment of new molecular tools to improve the diagnosis of pancreatic cancer at an earlier stage.

Furthermore, to allow cost-effective screening, new methods using molecular tools, such as the analysis of telomerase changes, should be developed – focused on a simultaneous screening test for diverse cancers [59], and a second method directed to a more specific cancer such as methylated CpG islands in pancreatic cancer-related genes.

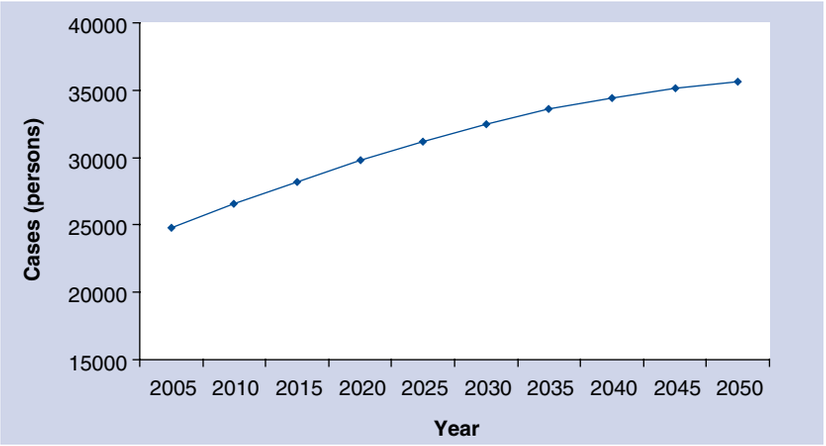

Figure 2. Projections of pancreatic cancer cases in Latin America 2005–2050. Tendency based on an incidence of 4.5/100,000 persons and the Latin American population projections of: Economic Commission for Latin America and the Caribbean; Latin American and Caribbean Demographic Centre (CELADE) – Population Division; Demographic Bulletin (July 2004). This graph is based on the full calculated anticipated population growth, without adjusting for smoking incidence rate.

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Executive summary

Current situation

- Pancreatic cancer is the ultimate gastrointestinal cancer challenge, for all stages combined. The 1-year survival rate is approximately 20%, and the overall 5-year survival rate has remained dismally poor at less than 5%.
- The most useful tumor marker for pancreatic adenocarcinoma is still the carbohydrate antigen 19–9.
- The only curative treatment for pancreatic cancer is complete surgical resection.

New options

- The development of new tumor markers, epigenetics and molecular tools offer the hope to reach an early diagnosis of pancreatic cancer.
- One strategy to improve the diagnosis should be detection in first screening of molecular changes common to diverse gastrointestinal malignancies, such as shortage of telomer, and a second method to identify the primary pancreatic cancer.

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