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REVIEW

Advances in diagnosis, treatment and palliation of pancreatic carcinoma: 1990-2010

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Abstract

Several advances in genetics, diagnosis and palliation of pancreatic cancer (PC) have occurred in the last decades. A multidisciplinary approach to this disease is therefore recommended. PC is relatively common as it is the fourth leading cause of cancer related mortality. Most patients present with obstructive jaundice, epigastric or back pain, weight loss and anorexia. Despite improvements in diagnostic modalities, the majority of cases are still detected in advanced stages. The only curative treatment for PC remains surgical resection. No more than 20% of patients are candidates for surgery at the time of diagnosis and survival remains quite poor as adjuvant therapies are not very effective. A small percentage of patients with borderline non-resectable PC might benefit from neo-adjuvant chemoradiation therapy enabling them to undergo resection; however, randomized controlled studies are needed to prove the benefits of this strategy. Patients with unresectable PC benefit from palliative interventions such as biliary decompression and celiac plexus block. Further clinical trials to evaluate new chemo and radiation protocols as well as identification of genetic markers for PC are needed to improve the overall survival of patients affected by PC, as the current overall 5-year survival rate of patients affected by PC is still less than 5%. The aim of this article is to review the most recent high quality literature on this topic.

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Key words: Diagnosis; Epidemiology; Palliation; Pancreatic cancer; Therapy

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INTRODUCTION

The vast majority (90%) of pancreatic cancers (PC) are malignant tumors originating from pancreatic ductal cells[1]. Anatomically, 78% of PCs are located in the head, and the remaining 22% are equally distributed in the body and in the tail[2]. The most common clinical presentations are progressive weight loss and anorexia, mid abdominal pain and jaundice[3-5]. Over the past two decades many advances in the diagnosis, therapy and palliation of PC have taken place although the overall survival of affected patients has not improved significantly. The aim of this article is to review the most recent high quality literature on this topic.

SEARCH STRATEGY AND SELECTION CRITERIA

The literature search was targeted at studies that reported at least one of the following aspects of PC: epidemiology, diagnosis, therapy (e.g. surgery, radiotherapy, chemotherapy) and palliation. Randomized controlled trials (RCT) and prospective observational studies were given preference. Each of the topics was searched in MEDLINE, Ovid MEDLINE In-process, Cochrane Database of Systematic Reviews, Database of Systematic Reviews, Database of Abstracts of Review of Effects, EMBASE, PubMed, National Library of Medicine Gateway by established systematic review methods (Jadad Scale for RCT, as well as Downs and Black checklist for observational studies)[6-8]. Articles from the authors' libraries and reference lists were further reviewed. We limited our search to English-language articles published from January 1990 to September 2010. We then developed a comprehensive and current database to catalog the medical literature on PC. To identify all potential papers, we searched the medical subject headings reported in Table 1. Three authors (Sharma C, Eltawil KM and Molinari M) independently performed the selection of the articles based on the content of titles and abstracts. When in doubt, each article was reviewed entirely. The decision to include articles in this review was reached by consensus. For conciseness, a full list of search strategies, search results, and quality assessment for each included study are available on request from the corresponding author.

EPIDEMIOLOGY

PC is the fourth leading cause of cancer related mortality in the United States with an estimated 42 500 new cases and 35 000 deaths from the disease each year[9]. In industrialized countries, the incidence of PC (11 per 100 000 individuals) ranks second after colorectal cancer among all gastrointestinal malignancies[10]. While the mortality rate for males has decreased by 0.4% from 1990 to 2005, the mortality rate for females has increased by 4.4%[9]. More than 80% of PCs are diagnosed in patients older than 60 and almost 50% have distant metastases at the time of presentation[10-12]. Men are more frequently affected than women [relative risk (RR) = 1.3] and individuals of African American descent in comparison to Caucasians (RR = 1.5)[10]. Analysis of overall survival shows that the prognosis of PC is still quite poor despite the fact that 1-year survival has increased from 15.2% (period between 1977-1981) to 21.6% (period between 1997-2001) and 5-year survival has increased from 3% (period between 1977-1986) to 5% (period between 1996-2004)[10].

RISK FACTORS

Smoking

The risk of PC in smokers ranks second to lung cancer[13] and it is proportionate to the frequency [≥ 30 cigarettes per day: odds ratio (OR) = 1.75], duration (≥ 50 years: OR = 2.13) and cumulative smoking dose (≥ 40 pack/years: OR = 1.78)[14]. A meta-analysis of 82 studies from 4 continents has shown that cigarette smokers were diagnosed at significantly younger age and had a 75% increased risk of developing PC in comparison to the regular population[15] and the risk persisted for 5 to 15 years after cessation[16]. In a case-control study of 808 PC patients matched against 808 healthy controls, female smokers were at increased risk in comparison to males as they suffered from a synergistic interaction between cigarette smoking, diabetes mellitus (OR = 9.3) and family history of PC (OR = 12.8)[17].

Diabetes

Nearly 80% of PC patients have either frank diabetes or impaired glucose tolerance[18]. Diabetes is usually diagnosed either concomitantly or during the two years preceding the diagnosis[19]. Several studies have assessed the role of diabetes in PC with conflicting results. A meta-analysis of 11 cohort studies found that the relative risk for diabetics was 2.1 [95% confidence interval (95% CI): 1.6-2.8][20]. These findings were supported by another cohort study of 100 000 Danish diabetic patients which found a standardized incidence ratio of 2.1 (95% CI: 1.9-2.4) in a 4-year follow-up[21]. A large prospective cohort study of 20 475 men and 15 183 women in the United States, has shown that the relative risk of PC mortality adjusted for age, race, cigarette smoking, and body mass index (BMI) was proportionate to the severity of abnormal glucose metabolism: RR was 1.65 for post load plasma glucose levels between 6.7 and 8.8 mmol/L; 1.60 for levels between 8.9 and 11.0 mmol/L, and 2.15 for levels equal or more than 11.1 mmol/L[22]. Diabetes can be an early manifestation of PC as about 1% of new onset of diabetes in patients older than 50 is linked to PC[23], but there is no evidence that screening for recent onset diabetes would reduce the mortality[12] or lead to early diagnosis[24].

The link between abnormal glucose and PC exists only for type Ⅱ diabetes. A meta analysis of 36 studies has shown that the OR of PC for patients with type Ⅱ diabetes for more than 5 years was 2.1[25], while there are no reports on the association between PC and type I diabetes[26].

Family history of diabetes does not appear to be a risk for PC. Compared to subjects with no family history, diabetics with a positive family history have an OR of 0.8 while non-diabetics with a positive family history have an OR of 1.0[27].

A recent prospective study found that women with gestational diabetes have a relative risk of PC of 7.1 (95% CI: 2.8-18.0)[28]. Gapstur and colleagues have proposed a mechanism to explain these findings[22] by the fact that at high levels, insulin binds to the insulin-like growth factor I (IGF1) receptor[24] and downregulates IGF binding protein 1[25] causing an increase in cell growth in PC cell lines[29,30].

Alcohol

The role of alcohol is controversial and several studies

Table 1 Summary of the terms used singly or in combination for evidence acquisition

Primary MeSH terms	Secondary MeSH terms (epidemiology, diagnosis)	Secondary MeSH terms (treatment, palliation)
Pancreatic neoplasm(s)	Epidemiology	Pancreaticoduodenectomy
Adenocarcinoma(s)	Classification	Resection
Carcinoma(s)	Diagnosis	Therapeutic(s)
Pancreatic diseases	Differential diagnosis	Treatment outcome(s)
Pancreas	Risk factor(s)	Surgery
Carcinoma, pancreatic ductal	Diagnostic imaging	Surgical procedures
Pancreatic duct(s)	Magnetic resonance imaging	Clinical trial(s)
Humans	Endosonography	Controlled clinical trial(s)
Adult	Ultrasonography	Randomized controlled trial(s)
	Emission computed tomography	Clinical trial (phase Ⅰ)
	Radionuclide imaging	Clinical trial (phase Ⅱ)
	Positron emission tomography	Clinical trial (phase Ⅲ)
	Tomography	Clinical trial (phase Ⅳ)
	X-ray computed	Drug therapy
	Biopsy (fine needle)	Chemotherapy
	Biopsy (needle)	Neoadjuvant therapy
	Cytology	Adjuvant
	Cytodiagnosis	Antineoplastic combined chemotherapy protocols
	Tumor markers (biological) antigen(s)	Antineoplastic agent(s)
	Carcinoembryonic antigen	Antimetabolites, antineoplastic
	Ca 19-9 antigen	Combined modality therapeutic antineoplastic
	Ca 125 antigen	Combined chemotherapy protocols neoadjuvant
	Antigens, tumor-associated, carbohydrate	Therapy
	Endoscopic retrograde cholangiopancreatography	Radiotherapy
	Computed assisted image processing	Drainage
	Sensitivity and specificity	Cholestasis
	Endoscopy	Obstructive jaundice
		Celiac plexus
		Autonomic nerve block
		Nerve block
		Ethanol
		Injections, intralesional
		Cisplatin
		Deoxycytidine
		Epidermal growth factor
		Fluorouracil
		Endostatin
		Biological products
		Neoplasm proteins
		Immunotherapy
		Antibodies, monoclonal

have shown inconsistent findings. This might be attributed to multiple associations with confounding variables mainly smoking, socio-economic status[31] and pancreatitis[30]. A recent pooled analysis of 14 cohort studies with a sample of 862 664 individuals has shown a slight positive association between PC and alcohol intake only for consumption above 30 g/d (RR = 1.22; 95% CI: 1.03-1.45)[32]. Contrasting findings were reported by a European epidemiological study with a smaller sample size (n = 555) that did not show any association between PC and alcohol consumption[33].

Compared with light drinkers, men consuming large amounts of hard liquor suffered from a 62% increased risk of PC (95% CI: 1.24-2.10)[16,34], but this was not observed for women or for beer and wine drinkers[34].

Although moderate alcohol consumption is not a risk factor, African Americans were found to have a significantly higher OR when adjusted for their drinking habits, suggesting that racial differences might play a role in the development of PC[35].

Pancreatitis

Several studies have shown a positive association between PC and history of pancreatitis, although the magnitude is still controversial[36,37]. An international epidemiological study reported that both genders with chronic pancreatitis had an increased risk independently of the cause of pancreatitis[37]. A large case-control study showed that chronic pancreatitis lasting more than 7 years was associated with a higher risk of PC (RR = 2.04; 95% CI: 1.53-2.72)[38]. A large Italian study from 1983 to 1992 found similar results, as the risk increased after 5 or more years of chronic pancreatitis (RR in the first 4 years = 2.1, RR after 5 years = 6.9)[34]. These findings have been challenged by an international study, as the risk was significantly increased only in the early years after diagnosis. This would suggest that pancreatitis might represent a manifestation of PC that becomes apparent only several years later, rather than a risk factor. The risk of PC in chronic pancreatitis has been shown to be especially true for patients affected by hereditary pancreatitis, who were found to have 53 times

the risk in comparison to normal individuals[39]. This was confirmed by another study that estimated a 40% cumulative risk of PC in patients with hereditary pancreatitis by the age of 70. For patients with paternal inheritance, the cumulative risk of PC was even higher with risk up to 75%[40]. Cytokines, reactive oxygen molecules and pro-inflammatory compounds seem to be responsible, as inflammation is a risk factor for many other solid tumors[38].

Genetic predisposition for PC

Genetic predisposing factors have been a topic of intense research in the last decades. Case reports of families with multiple affected members suggest that PC might have a hereditary background[41]. Yet, a large population study on twins identified hereditary factors for prostatic, breast and colorectal cancers, but not for PC[42]. A Canadian study on patients with suspected hereditary cancer syndromes found that the standardized incidence rate of PC was 4.5 (CI 0.54-16.) when cancer affected one 1st degree relative, and increased to 6.4 (CI 1.8-16.4) and 32 (CI 10.4-74.7) when two and three 1st degree relatives were affected, respectively[43]. This translates to an estimated incidence of PC of 41, 58 and 288 per 100 000 individuals, respectively, compared to 9 per 100 000 for the general population[44].

Brentnall *et al*[45] and Meckler *et al*[46] described examples of autosomal dominant PC in individuals presenting at early age (median age 43 years) and with high genetic penetrance (more than 80%). A mutation causing a proline (hydrophobic) to serine (hydrophilic) amino acid change (P239S) within a highly conserved region of the gene encoding paladin (PALLD) was found in all affected family members and was absent in non-affected individuals of the same family (family X). Another study has shown that the P239S mutation was only specific for family X and was not a common finding in other individuals with suspected familial PC[47]. Currently, genetic predisposition is thought to be responsible for 7% to 10% of all PC[48]. Genetic factors including germline mutations in p16/CDKN2A[49], BRCA2[50-52] and STK 11[53] genes increase the risk of PC. The combination of all these known genetic factors accounts for less than 20% of the familial aggregation of PC, suggesting the role of other additional genes.

A systematic review and meta analysis of studies that quantified familial risk of PC has shown that individuals with positive family history have an almost two-fold increased risk (RR = 1.80, CI 1.48-2.12)[54]. Therefore, families with two or more cases may benefit from a comprehensive risk assessment involving collection of detailed family history information and data regarding other risk factors[55]. A case-control study of PC in two Canadian provinces (Ontario and Quebec) assessed a total of 174 PC cases and 136 healthy controls that were compared for their family histories of cancer. Information regarding the ages and sites of cancer was obtained in 966 first degree relatives of the PC patients and for 903 first degree relatives of the control group. PC was the only malignancy in excess in relatives of patients with PC, compared to the control group (RR = 5, $P = 0.01$). The lifetime risk of PC was 4.7% for the first degree relatives and the risk was 7.2% for relatives of patients diagnosed before the age of 60[56].

Besides the isolated aggregation of PC in some families, several other hereditary disorders predispose to PC in known familial cancer conditions[57]. These include hereditary pancreatitis, Puetz-Jeghers syndrome, familial atypical multiple mole melanoma, familial breast and ovarian cancer, Li-Fraumeni syndrome, Fanconi anaemia, Ataxia-telangiectasia, familial adenomatous polyposis, cystic fibrosis and possible hereditary non-polyposis colon cancer or Lynch syndrome[11,55,58-60].

Familial PC registries

As the prognosis of PC is generally poor, there has been a strong interest in detecting genes or other markers that could help identify high risk patients at an early stage. Although a precise genetic marker for this scope is not currently available, geneticists and epidemiologists have been profiling traits of high risk families enrolled in registries established in North America and Europe[61]. Even if there is no standardized definition for familial PC, most authors apply the term to families with at least two first degree relatives affected by PC in the absence of other predisposing familial conditions[61]. The creation of familial PC registries has been used not only for identification of genetic mutations, but also for the screening of high risk individuals. In selected centers in North America and Europe, screening programs for high risk individuals have been implemented with the use of endoscopic ultrasound (EUS) and computed tomography (CT) scanning or magnetic resonance imaging (MRI). Such early diagnosis of PC within a comprehensive screening program is hoped to ultimately result in improved survival[62]. The discovery of the genetic bases of inherited PC continues to be an active area of research, and in 2001 a multi-center linkage was formed to conduct studies aimed at the localization and identification of PC susceptibility genes (PACGENE)[63]. The complex nature of pedigree data makes it difficult to accurately assess risk based upon the simple counting of the number of affected family members, as it does not adjust for family size, age of onset of PC, and the exact relationship between affected family members. Therefore, computer programs have been developed to integrate these complex risk factors and pedigree data. In April 2007, the 1st risk prediction tool for PC, PanaPro was released[64]. This model provides accurate risk assessment for kindreds with familial PC as the receiver operating characteristic (ROC) curve was 0.75 which is considered good for predictive models.

Nutritional status

A number of studies have explored the relationship between BMI, lifestyle, diet and the risk of PC, but uncertainty regarding the strength of this relationship still exists. A recent case-control study of 841 patients and 754 healthy controls showed that individuals with a BMI of 25-29.9 had an OR of 1.67 (95% CI: 1.20-2.34) in comparison to obese patients (BMI of $\geqslant 30$) who had an OR of 2.58 (95% CI: 1.70-3.90) independently of their diabetes status[65]. The duration of being overweight was

Table 2 Known risk factors for pancreatic cancer

Age (more than 60 yr)
Smoking
Diabetes
Type II
Gestational diabetes
Impaired glucose tolerance
Alcohol
Pancreatitis
Acute
Chronic
Genetic predisposition
Family history
Hereditary disorders
Hereditary pancreatitis
Puetz-Jeghers syndrome
FAMMM
Familial breast and ovarian cancer
Li-Fraumeni syndrome
Fanconi anaemia
Ataxia-telangiectasia
Familial adenomatous polyposis
Cystic fibrosis
HNPCC
Lynch syndrome
Obesity

FAMMM: Familial atypical multiple mole melanoma; HNPCC: Hereditary non polyposis colon cancer.

significantly longer among patients with PC than controls. Being obese or overweight, particularly in early adulthood, resulted in earlier onset of PC (age at presentation of PC was 61 years for overweight patients and 59 years for obese) when compared to the median age of diagnosis (64 years) in the general population[66]. A number of studies reported that central weight gain measured by waist circumference and/or waist-to-hip ratio had a statistically significant increased risk compared to those with peripheral weight gain (RR = 1.45, 95% CI: 1.02-2.07)[67,68]. The known risk factors for PC are summarized in Table 2.

CLASSIFICATION

Anatomical classification

According to the location, PC can be divided in three groups: tumors of the head, body and tail. PCs of the head are at the right side of the superior mesenteric vessels, and tumors of the neck and body are located between the superior mesenteric vessels and the inferior mesenteric vein. PCs of the tail are located to the left of the inferior mesenteric vein.

A large epidemiological study[2] of 100,313 patients in the United States has shown that 78% of PC presents in the head, 11% in the body and 11% in the tail (Figure 1).

Pathological classification

Recent advances in surgical pathology techniques integrated with molecular biology have allowed advances in the modern classification of PC. A summary of the clinicopathological features of the different categories of PC is shown in Table 3.

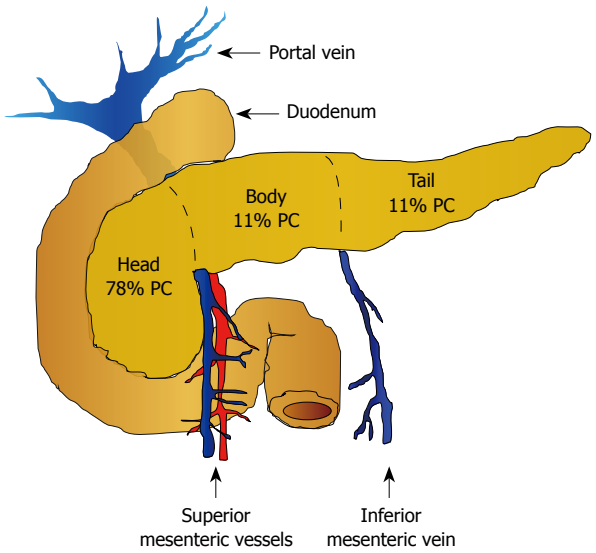

Figure 1 Graphical representation of the pancreas and frequency of pancreatic cancer in the three anatomical sections: head, body and tail. PC: Pancreatic cancer.

Ductal infiltrating adenocarcinoma

Ductal infiltrating adenocarcinoma (DIA) represents the most common type (85%-90%) of PC originating from ductal epithelial cells. Most DIAs appear as whitish masses, hard at palpation and poorly defined from surrounding tissues, predominantly solid although cystic degenerations can be seen in larger tumors[89]. The microscopic appearance of DIA ranges from well-differentiated neoplasms difficult to distinguish from reactive gland, to poorly differentiated. The majority of DIAs are moderately to poorly differentiated and develop a dense desmoplastic stroma[89]. Mutations in the KRAS2 or p16/CDKN2A genes are observed in 90% of patients, TP53 gene abnormalities in more than 75% and more than 55% of cases have changes in MADH4/DPC4 genes. Tumors showing loss of DPC4 expression have a worse outcome than those with intact DPC4[90], and immunolabeling for DPC2 protein can help to classify metastatic carcinomas of unknown primary etiology[91].

Solid pseudopapillary neoplasm

Solid pseudopapillary neoplasms (SPPN) represent a small proportion of PCs (3%) and present as solid, or solid and cystic masses. They are malignant epithelial neoplasms made of poorly cohesive cells that form pseudo-papillae around the blood vessels[91]. The majority of SPNN are grossly well demarcated, but typically do not have a well formed capsule. The majority are solid, yellowish and soft[92]. Larger tumors usually develop cystic degeneration filled with blood and necrotic debris. Cases that are almost completely cystic without a solid component have also been reported[91].

Molecular analyses have shown that SPNN are different from ductal adenocarcinomas as they do not harbor mutations in the Kras 2, p16/CDKN2A, TP53, MADH4/DPC4 genes[93]. In contrast, 90% of SPNN have a mutation on chromosome 3p (CTNNB1) respon-

Table 3 clinico-pathological features of the most frequent classes of pancreatic cancer

Classification	Frequency (%)	Author	yr	Survival (5-yr survival after surgical resection)
DIA (incidence per 100000 patients at risk = 8.37)[69]	85-90[1]	Conlon *et al*[70]	1996	10%
		Winter *et al*[71]	2006	18%
		Poultsides *et al*[72]	2010	19%
SPPN (incidence per 100000 patients at risk = NA)[69]	0.1-3[73]	Papavramidis *et al*[74]	2005	95%
IPMN (incidence per 100000 patients at risk = 0.03)[69]		Shin *et al*[76]	2010	Benign: 95% Malignant: 64%
IPMN with simultaneous DIA: (incidence per 100000 patients at risk = NA)[69]	5[75]	Poultsides *et al*[72]	2010	42%
		Fan *et al*[77]	2010	57%
		Sohn *et al*[78]	2004	43%
Pancreatoblastoma (incidence per 100000 patients at risk = NA)[69]	0.50[79]	Dhebri *et al*[80]	2004	50%
		Saif *et al*[79]	2007	80%
Undifferentiated (incidence per 100000 patients at risk = 0.03)[69]	2-7[81]	Paal *et al*[82]	2001	3% (3-yr survival)
		Connolly *et al*[83]	1987	5 mo (average survival)
Medullary carcinoma (incidence per 100000 patients at risk = NA)[69]	NA	Wilentz *et al*[84]	2000	11% 14 mo (average survival)
Mucinous cystadenocarcinoma (incidence per 100000 patients at risk = 0.43)[69]	1	Ridder *et al*[85]	1996	56%
Adenosquamous carcinoma (incidence per 100000 patients at risk = 0.05)[69]	4	Madura *et al*[86]	1999	5-7 mo (median survival)
		Mulkeen *et al*[87]	2006	
Acinar cell carcinoma (incidence per 100000 patients at risk = 0.02)[69]	2	Holen *et al*[88]	2002	38 mo after surgical resection (median survival) 14 mo for unresectable disease (median survival)

DIA: Ductal infiltrating adenocarcinoma; SPPN: Solid pseudo-papillary neoplasm; IPMN: Intraductal papillary nucinous neoplasm; NA: Not applicable.

sible for the metabolism of β-catenin protein causing its accumulation in the cytoplasm and nucleus of neoplastic cells[94]. As a result alteration in β-catenin protein expression disrupts E-cadherin which is a key regulator of cell junctions causing poor adhesion of neoplastic cells[95]. Although there is some histological overlap between SPNN and other tumors of the pancreas, immunolabeling for β-catenin protein may help establish the diagnosis.

Intraductal papillary mucinous neoplasm

Intraductal papillary mucinous neoplasms (IPMNs) represent 5% of all PCs and are papillary epithelial mucin-producing neoplasms arising in the main pancreatic duct or in one of its branches. IPMNs are relatively common with increasing age of the population[91] and the mean age at presentation is 65 years[96]. IPMN is a potential pre-malignant condition and the risks of developing invasive adenocarcinoma increase with tumor size and when originating in the main pancreatic duct.

Adenocarcinoma is present in up to one-third of patients with IPMN and current guidelines recommend surgical resection when IPMNs are greater than 3 cm, in the presence of main pancreatic duct dilatation and when mural nodules are detected[97].

Neoplastic cells of IPMN are columnar with gene profiles similar to infiltrating ductal carcinoma. About 25% of patients show loss of heterozygosity of the STK11/LKB1 gene[98,99]. Other frequent gene mutations are TP53, KRAS2, and P16/CDKN2A[100].

Pancreatic intraepithelial neoplasia

Pancreatic intraepithelial neoplasia (PanIN) represents a neoplastic proliferation of mucin producing epithelial cells confined to the smaller pancreatic ducts and is considered a precursor to invasive ductal carcinoma[101].

PanINs are usually characterized by lesions too small to be symptomatic or to be detected by current imaging technologies[89]. Microscopically, PanINs are classified into three grades (PanIN-1, PanIN-2 and PanIN-3) based on the progressive degree of architecture abnormality and cellular atypia[102]. PanIN-1 shows minimum cellular atypia, PanIN-2 moderate changes and PanIN-3 is equivalent to PC-*in-situ*. The discovery of specific molecular changes present in both PanIN and PC has helped to establish that these small lesions are the precursors to DIA[103]. Early abnormalities of IPMNs are telomerase shortening and activating point mutations in the KRAS2 gene while intermediate mutation is the activation of the p16/CDKN2A gene and late events are alterations in the TP53, MADH4/DPC4, and BRCA2 genes[102]. The understanding that many DIAs arise from PanIN lesions has prompted screening efforts on the detection of these small and potentially curable lesions[104].

Pancreatoblastoma

Pancreatoblastoma is a rare malignant tumor (0.5% of PC) usually presenting in the pediatric age group. Generally, it appears as a soft and well demarcated mass with epithelial or acinar differentiation, but often it has cells with endocrine and mesenchymal characteristics[79]. Most pancreato-blastomas affect children with a mean age of 5 years and are frequently associated with elevated levels of serum alpha fetoprotein. The median survival of patients with pancreato-blastomas is 48 mo and the 5-year

survival rate after successful resection is 50% (95% CI: 37%-62%)[80,105].

The majority of pancreato-blastomas have loss of heterozygosity of chromosome 11p from the maternal side[106]. These molecular findings unite pancreatoblastoma with other primitive neoplasms such as hepatoblastoma and nephroblastoma[107]. Genetic alterations in the adenomatous polyposis coli (APC)/β-catenin pathway have also been detected in most pancreato-blastomas including mutations in β-catenin (CTNNB1) and APC genes[107].

Undifferentiated carcinoma

Undifferentiated PC (UPC) lacks differentiation direction[91] and presents with symptoms similar to patients with DIA, but has a worse prognosis as it has a more aggressive behavior and tends to metastasize and infiltrate surrounding organs in early stages[82]. The average time from diagnosis to death is about 5 mo and only 3% of patients are alive at 5 years after undergoing surgical resection. UPCs can form large locally aggressive masses and may present with severe hemorrhage and necrosis. The majority of UPCs have KRAS2 gene mutation suggesting that they arise from pre-existing ductal adenocarcinomas that transform into poorly differentiated tumors during their progression[108].

Medullary carcinoma

Medullary carcinoma (MC) is a variant of PC characterized by poor differentiation and syncytial growth that has been described and recognized only in recent years[84]. Patients with MC have a better prognosis and are more likely to have a family history of any kind of cancer[109]. MC does not differ significantly from other classes of PC in its clinical presentation, age and gender. These tumors tend to form well demarcated soft masses and microscopically they are usually poorly differentiated with pushing rather than infiltrating features[110]. Focal necrosis and intratumoral lymphocytic infiltration can be prominent similar to MC of the colon and other tumors with microsatellite instability[89]. MCs have been shown to have loss of expression of one of the DNA mismatch repair proteins (M1h1 and Msh2) and mutation in the BRAF gene, which is a downstream effector of the k-ras pathway[111]. Patients with MC and their families may benefit from genetic counseling and more frequent screening for early detection of other common cancers. The prognosis of MC is better than adenocarcinoma, although it is not responsive to adjuvant chemotherapy based on fluorouracil (5-FU), similar to colon cancer with microsatellite instability[112].

Other rare classes of PCs

Mucinous cystadenocarcinoma: Malignant cystic neoplasms are rare entities that account for only 1% of all pancreatic tumors[113]. Both serous and mucinous cystic neoplasms are tumors of the exocrine pancreas with different biological behaviors. Serous cystadenomas are considered benign tumors with almost no malignant potential often managed expectantly unless symptomatic. However, the preoperative differentiation between a benign serous cystadenoma and malignant serous cystadenocarcinoma remains difficult[114]. Histologically, cystadenocarcinomas appear identical to serous cystadenomas and are distinguished only by the presence of lymphovascular invasion or metastases[115]. Mucinous cystadenocarcinomas resemble DIAs although some cell populations can present with undifferentiated features and other histological characteristics such as osteoclast-like giant cells, adenosquamous carcinoma, choriocarcinoma, or high-grade sarcoma[116-119]. Mucinous cystic neoplasms of the pancreas are slowly growing and only about 20% show invasive features[120,121].

The prognosis of cystadenocarcinoma is favorable compared to DIA with 5-year survival rates of 56% after radical resection[85]. There is limited evidence on the role of chemotherapy for cystadenocarcinomas of the pancreas as they appear to be unresponsive to current chemotherapy agents and radiation therapy[122,123].

Adenosquamous carcinoma: Adenosquamous carcinoma has previously been referred as adenoachantoma, mixed squamous and adenocarcinoma, and mucoepidermoid carcinoma. Histologically, they are characterized by mixed populations of adenomatous cells and cells with varying amount of keratinized squamous features. Usually this tumor affects patients in their seventh decade of life, with symptoms and pancreatic distribution similar to DIAs. Although it is reported that adenosquamous carcinomas represents 4% of all PCs (range 3%-11%), the literature on the natural history and survival is limited to case series only[86]. The prognosis seems to be worse than DIAs, with a mean survival of 5-7 mo even after surgical resection[86,87]. Lymphovascular and perineural invasion appear to be common and early features of adenosquamous carcinomas and the role of adjuvant chemo and radiation therapy is still not clear[124].

Acinar cell carcinoma: Acinar cell carcinomas (ACCs) represent less than 2% of all pancreatic malignancies[87,88]. ACCs are predominantly constituted by neoplastic cells with immunohistochemical staining characteristic for exocrine enzymes such as trypsin, chymotripsin or lipase, and they present in older patients than DIAs and the prognosis is slightly better, although the literature is somewhat limited[125,126]. Symptoms at presentation are aspecific and include abdominal pain and weight loss that are similar to all other PCs[125]. Very rarely, patients with ACC can develop subcutaneous fat necrosis secondary to exceedingly high concentrations of serum lipase and contrary to DIAs, bile duct obstruction causing jaundice is not as common[125]. Median survival for ACC confined to the pancreas treated by surgical resection is 38 mo, whereas it is 14 mo for individuals with unresectable disease[88]. For the majority of patients, surgical management is not curative as distant recurrent disease is more frequent than in DIA, suggesting the presence of early micrometastases even when the tumors are in the early stages[88]. Because ACCs are rare, there is a lack of studies on the role of chemotherapy, although radiation therapy seems to provide good responses in patients with regional unresectable disease[88].

DIAGNOSIS

Clinical presentation

Early symptoms of PC are notoriously difficult to measure as educational and economic factors influence their perception and reporting[127,128]. Cholestatic symptoms are more common in early PC of the head, while abdominal and back pain are more common in patients with distal PC and in patients with tumors infiltrating peripancreatic nerve tissue[129]. The appearance of these symptoms usually indicates advanced disease (Table 4)[129,130].

Early symptoms are usually vague such as anorexia, moderate weight loss, and early satiety[131]. Diabetes might be a sign of PC particularly when presenting during or beyond the sixth decade of life in the absence of risk factors and family history[20]. Diabetes is detected in 60%[132] to 81%[133] of PC patients within two years of their diagnosis. Early detection is possible if symptoms raise clinicians' suspicion, as 25% of patients report upper abdominal discomfort up to 6 mo prior to their diagnosis[134,135].

In two European studies[128,130], weight loss was present in 66%-84% of patients, jaundice (bilirubin level > 3 mg/dL) in 56%-61%, recent onset of diabetes in 97% and distended palpable gall bladder in 12%-94%, energy loss in 86%, abdominal pain in 78%, back pain in 48%, nausea in 50%, clay-coloured stools in 54%, dark urine in 58%, jaundice in 56% and pruritis in 32% of patients.

Serum tumor markers

Several serum tumor markers are associated with PC, however, to date, no single marker has been found to be optimal for screening.

Carbohydrate antigen 19-9: Carbohydrate antigens have been used as markers for several cancers[136,137]. The production of these antigens seems to be caused by the up-regulation of glycosyl transferase genes[138]. Among these carbohydrate antigen epitopes, Sialyl Lewis^a (sLe^a) detected by the 1116NS19-9 monoclonal antibody is commonly called carbohydrate antigen 19-9 (CA19-9)[139]. The serum levels of CA19-9 at the time of diagnosis and during follow-up of PC provide useful diagnostic and prognostic information[140,141]. Its sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are 70%-90%, 43%-91%, 72% and 81%, respectively[142-145]. A worse survival was observed in patients with pre-operative CA19-9 levels above 370 U/mL (median survival 4.4 mo *vs* 9.5 mo if CA19-9 < 370 U/mL, *P* value < 0.01)[146]. In another study, serum levels of CA19-9 > 200 U/mL were associated with a survival rate of 8 mo compared to 22 mo for patients with lower tumor antigen levels ($P < 0.001$)[147]. In a prospective study of patients undergoing curative resection for PC, post-operative CA19-9 < 37 U/mL was associated with a longer median and disease-free survival compared to the control group[148-150]. One of the limitations of CA19-9 is that high serum bilirubin can falsely increase its level and therefore the risk of false positive results in patients with jaundice. This is not observed for other markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 242 (CA 242)[141].

Table 4 Presenting symptoms of advanced pancreatic cancer

Symptom	Percentage
Abdominal pain	78-82
Anorexia	64
Early satiety	62
Jaundice	56-80
Sleep disorders	54
Weight loss	66-84
Diabetes	97
Back pain	48
Nausea and weight loss	50-86

CEA: CEA is part of a subgroup of glycoproteins functioning as intracellular adhesion molecules. CEA was first detected in pancreatic secretions, and several studies have shown high levels of CEA in the pancreatic juice of patients with PC[151-153]. A Japanese study found significantly higher CEA levels in the pancreatic juice of PC patients compared to those with benign pancreatic diseases. When the CEA cut off level in pancreatic juice was 50 ng/mL, the PPV, NPV, and the accuracy for diagnosis of carcinoma were 77%, 95% and 85%, respectively. CEA levels in pancreatic juice were higher in smaller tumors in comparison to advanced PC due to the incomplete obstruction of the pancreatic duct[154]. A recent study examining single *vs* combined efficacy of tumor markers showed that CEA (> 5 ng/mL) alone had a sensitivity of 45% and a specificity of 75% in comparison to CA19-9 which had a sensitivity of 80% but lower specificity (43%) ($P = 0.005$)[141,155]. The combination of CEA (> 5 ng/mL) and CA 19-9 (> 37 U/mL) decreased the sensitivity to 37%, but increased the specificity to 84%. Similarly, the combination of CEA (> 5 ng/mL) and CA242 (> 20 U/mL) decreased the sensitivity to 34% and increased the specificity to 92%. Yet, CEA and CA242 are currently not used as single tumor markers for PC, and the simultaneous use of CEA and CA19-9 provides the same information as CA19-9 alone[156-158].

CA 242: CA 242, a sialylated carbohydrate was first defined by Lindholm *et al* in 1985 and has been used for diagnostic and prognostic purposes[159,160]. For PC, its diagnostic sensitivity and specificity are 60% ($P = 0.073$) and 76% ($P = 0.197$), respectively, comparable to CEA. It also seems to be valuable in differentiating PC from benign pancreatic tumors as well as other hepatobiliary cancers and to predict outcomes as survival rates in CA 242 positive patients are lower than those with negative serum levels ($P = 0.002$)[141].

In a study comparing CA 242 and CA19-9[161], CA 242 appeared to be an independent prognostic factor for patients with resectable disease as serum levels of CA 242 < 25 U/mL were associated with a significantly better survival ($P < 0.05$). For patients with unresectable disease, poorer outcomes were observed when CA 242 levels were > 100 U/mL.

Similar results have been confirmed by Ni *et al*, who found that CA 242 is an independent prognostic factor

Table 5 Summary of the performance characteristics of serum tumor markers for the diagnosis of pancreatic cancer

Serum tumor marker	Author	Yr	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
CA19-9	Boeck *et al*[141]	2006	70-90	43-91	72	81	67
	Ni *et al*[142]	2005					
	Steinberg *et al*[143]	1990					
	Safi *et al*[144]	1997					
	Mu *et al*[162]	2003					
CEA in pancreatic juice	Ozkan *et al*[155]	2003	NA	NA	77	95	85
	Futakawa *et al*[154]	2000					
	Ni *et al*[142]	2005					
CEA in serum	Boeck *et al*[141]	2006	45	75	NA	NA	NA
CA19-9 + CEA	Ni *et al*[142]	2005	37	84	91	90	89
	Ozkan *et al*[155]	2003					
	Ma *et al*[163]	2009					
CA 242	Nilsson *et al*[160]	1992	60	76	63	61	71
	Röthlin *et al*[164]	1993					
	Carpelan-Holmström *et al*[165]	2002					
	Pålsson *et al*[166]	1993					
CEA + CA 242	Ni *et al*[142]	2005	34	92	67	90	87
	Ozkan *et al*[155]	2003					
	Hall *et al*[167]	1994					
CA19-9 + CA 242	Ni *et al*[142]	2005	59	77	65.3	87.8	65.1
	Röthlin *et al*[164]	1993					
	Jiang *et al*[158]	2004					
CA19-9 + CA 242 + CEA	Ni *et al*[142]	2005	29	96	NA	NA	NA

PPV: Positive predictive value; NPV: Negative predictive value; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; CA 242: Carbohydrate antigen 242; NA: Not applicable.

in PC yielding more information than CA 19-9[142,161]. In this study the use of combined tumor markers resulted in lower sensitivity, but higher specificity (Table 5). Despite these findings, CA 242 is not used in clinical practice as commonly as Ca 19-9 due to the limited number of laboratories equipped to run this test.

Other tumor markers

Recent studies have identified other serum molecules such as CA494[168], CEACAM1[169], PTHrP[170], TuM2-PK[171], CAM 17.1[172] and serum beta HCG[173] as potential markers for PC. Although preliminary results appear promising with sensitivity and specificity comparable and sometimes superior to CA19-9 and CEA, their clinical use has to be confirmed in larger studies and their role is currently confined to a limited number of medical centers and for research purposes.

Imaging modalities

Although PC may be detected with one particular diagnostic test, proper staging often requires the use of several imaging modalities[174].

Abdominal ultrasound: Trans-abdominal ultrasound (US) is currently used as a screening test for patients with suspected PC[175]. Its sensitivity ranges between 48%[176] and 89%[177], specificity between 40%[178] and 91%[179] and accuracy between 46%[176] and 64%[180]. PCs measuring less than 1 cm are detected by US in only 50% of cases, while the sensitivity increases to 95.8% for tumors larger than 3 cm[177]. Other factors affecting the sensitivity of US are the operator's experience[181] and the technical characteristics of the machine. Newer US machines such as tissue harmonic imaging decrease artefacts and improve tissue contrast and therefore diagnostic accuracy[182]. US has a relatively low performance profile for the staging of PC as its sensitivity for lymph node involvement only ranges between 8%[159] and 57%[177].

Color Doppler US has been used to assess the possible involvement of the portal vein and superior mesenteric vessels with a sensitivity ranging between 50%[183] and 94%[184], specificity between 80% and 100%[183] and accuracy between 81% and 95%[175].

The recent introduction of intravenous contrast has been shown to improve evaluation of the vascularity of pancreatic lesions allowing differentiation between PC and other conditions with 90% sensitivity, 100% specificity and 93% accuracy[185]. Currently, US is considered a useful imaging modality for the initial screening of PC based on its ability to document unresectability (PPV = 94%)[176]. However, the PPV for resectabiltiy is only 55%[186], therefore, other imaging techniques are usually employed for better staging.

EUS: EUS provides high resolution images of the pancreas without interference by bowel gas[187]. Despite the advancement of CT scans, EUS appears to have a higher sensitivity in detecting small PCs (98%) in comparison to CT (86%)[188]. EUS has higher sensitivity compared to CT for local tumor staging (67% *vs* 41%), similar sensitivity for lymph node involvement (44% *vs* 47%) and potential tumor resectability (68% *vs* 64%)[185]. EUS has a NPV of 100% for PC of the head[186,189] and an accuracy of 90% for the assessment of portal and splenic vein inva-

sion[178,190]. On the other hand, EUS does not appear to be accurate enough in assessing the invasion of SMA and superior mesenteric vein (SMV) with a NPV of 82% and sensitivity of only 50%[191,192].

In order to improve EUS performance in PC staging, recent studies have assessed the benefits of using parenteral contrast agents. This technique has shown 92% sensitivity, 100% specificity, 100% PPV, 86% NPV and 95% accuracy[193]. Although EUS is becoming a leading modality for staging and diagnosis of PC, drawbacks of this technique are the fact that it is invasive, highly operator dependent, costly and associated with a small risk of pancreatitis (0.85%)[194], bleeding and duodenal perforation.

CT: On contrast CT, PC appears as an ill-defined, hypoattenuating focal mass with dilatation of the upstream pancreatic and or biliary duct[174]. Optimum visualization of the pancreas requires imaging acquisition obtained during both arterial and portal phases[195]. Sensitivity and specificity of thin section triple phase helical CT is 77% and 100%, respectively, for lesions less than 2 cm[196]. In a multicentric trial, the diagnostic accuracy of CT for resectability was 73% with a PPV for non resectability of 90%[197].

With the advent of multi detector CT scanners (MDCT), the pancreas can be imaged at a very high spatial and temporal resolution[198,199]. The dual phase pancreatic protocol MDCT using 1 to 3 mm slice collimation is one of the most sensitive techniques for metastatic disease to the liver and peritoneum[186,200,201]. Recent studies have shown that MDCT has a NPV of 87% for tumor resectability compared to a NPV of 79% for conventional helical CT[202] and with an accuracy between 85% and 95%[203,204].

Images from MDCT can be used to visualize the biliary tree and normal vascular variants such as replaced hepatic arteries before surgical planning. Gangi *et al*[198] reported that pancreatic ductal dilatation in asymptomatic patients could be identified between 0 to 50 mo before PC diagnosis was confirmed. The sensitivity, specificity and accuracy of CT in the presence of hypo-attenuated pancreatic lesions, pancreatic ductal dilatation with cut-off, distal pancreatic atrophy, pancreatic contour abnormalities and common bile duct dilatation are reported in Table 6[205].

Despite these improvements, interpretation of the CT scan is quite challenging in the setting of pancreatitis forming mass effects[206] and in the presence of loco-regional lymph node involvement and small hepatic metastasis[207].

Magnetic resonance imaging-magnetic resonance cholangiopancreatography: In most institutions, MRI is performed when other imaging modalities provide insufficient data for the clinical staging of the tumor, or when treatment planning can not be based on the images obtained by other techniques. Several studies have shown that MRI is superior to CT for the detection and staging of PC (100% *vs* 94%, respectively)[208-211]. However, recent evidence has challenged this belief. The use of MRI-magnetic resonance cholangiopancreatography (MRCP) to better characterize PC is supported by a prospective analysis that compared these two modalities in patients with periampullary cancers[212]. MRI-MRCP was superior to CT in differentiating malignant from benign lesions (ROC = 0.96 *vs* 0.81, $P < 0.05$) and MRI-MRCP had better sensitivity (92% *vs* 76%), specificity (85% *vs* 69%), accuracy (90% *vs* 75%), PPV (95% *vs* 88%) and NPV (79% *vs* 50%) compared to CT. Another study confirmed the previous results with MRI-MRCP showing 97% sensitivity, 81% specificity and 89% accuracy[213].

Table 6 Sensitivity, specificity and accuracy of computed tomography findings in pancreatic cancer patients

CT finding	Sensitivity (%)	Specificity (%)	Accuracy (%)
Hypoattenuation	75	84	81
Ductal dilatation	50	78	70
Ductal interruption	45	82	70
Distal pancreatic atrophy	45	96	81
Pancreatic contour anomalies	15	92	70
CBD dilatation	5	92	67

CT: Computed tomography; CBD: Common bile duct.

On the other hand, other studies comparing gadolinium-enhanced MRI with MDCT have shown that MRI and CT had equivalent sensitivity and specificity (83%-85% *vs* 83% and 63% *vs* 63%-75%, respectively). Both techniques had good to excellent agreement between radiologists, although MRI had a superior agreement for the evaluation of distant metastases (inter-observer agreement between MRI and CT scan; 0.78 *vs* 0.59 $P = 0.1$)[214]. On the other hand, with the improvement in CT scan technology, recent studies have shown that MRI might have lower sensitivity in comparison to MDCT (82%-94% *vs* 100%)[215]. This was confirmed by a recent meta-analysis comparing the accuracy of several imaging modalities which showed that helical CT had superior sensitivity compared to MRI (91% *vs* 84%) and transabdominal US (91% *vs* 76%)[216]. Sensitivity for resectability of the tumor was equal for both MRI and helical CT (82% *vs* 81%, respectively)[216].

Positron emission tomography: ^{18}F-2fluoro-2-deoxy-D-glucose (FDG) accumulated by tumor cells provides positron emission tomography (PET) with the advantage of combining metabolic activity and imaging characteristics. Newly developed PET scanners can detect small PCs up to 7 mm in diameter and diagnose metastatic disease in about 40% of cases[217,218]. A Japanese study found that the overall sensitivity of PET-CT was superior to contrast CT (92% *vs* 88%) and that PET was better at detecting bone metastases (100% *vs* 12%). However, CT scanning was superior for the evaluation of vascular invasion (100% *vs* 22%), involvement of para aortic regional lymph nodes (78% *vs* 57%), identification of peritoneal dissemination (57% *vs* 42%) and hepatic metastases (73% *vs* 52%)[219]. Another Japanese study confirmed that PET had a sensitivity of 87%, a specificity of 67% and accuracy of 85%, and that tumors with metastatic

Table 7 Summary of the performance characteristics of imaging tests for the diagnosis of pancreatic cancer

Diagnostic modality	Author	Yr	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
US	Giovannini *et al*[176]	1994	48-95	40-91	92	100	46-64
	Böttger *et al*[177]	1998					
	Rösch *et al*[178]	1991					
	Niederau *et al*[179]	1992					
	Palazzo *et al*[180]	1993					
	Tanaka *et al*[231]	1996					
Doppler US	Candiani *et al*[232]	1998	50-94	80-100	79	88	81-95
	Casadei *et al*[184]	1998					
	Calculli *et al*[233]	2002					
EUS	Akahoshi *et al*[234]	1998	98	97	94	100	90
	Legmann *et al*[235]	1998					
Contrast enhanced US	Dietrich *et al*[185]	2008	90	100	100	86	93
CT	Bronstein *et al*[196]	2004	77	100	NA	NA	73
	Megibow *et al*[197]	1995					
MDCT	Park *et al*[214]	2009	83-91	63-75	80	87	85-95
	Vargas *et al*[202]	2004					
	Diehl *et al*[203]	1998					
	Schima *et al*[208]	2002					
MRI-MRCP	Andersson *et al*[212]	2005	83-92	63-85	95	79	89
PET	Maemura *et al*[217]	2006	87-100	67-77	94	100	85-95
	Delbeke *et al*[221]	1999					

PPV: Positive predictive value; NPV: Negative predictive value; US: Ultrasound; EUS: Endoscopic ultrasound; CT: Computed tomography; MDCT: Multi detector computed tomography; PET: Positron emission tomography; NA: Not applicable; MRI: Magnetic resonance imaging.

disease had significantly higher standardized uptake values [SUV = tissue concentration (millicuries/g)/injection dose (millicuries)/body weight (g)] than those without metastases[220]. PET had superior sensitivity (100% *vs* 65%), specificity (77% *vs* 61%), NPV (100% *vs* 31%), PPV (94% *vs* 87%) and accuracy (95% *vs* 65%) in an American study comparing PET-CT with a SUV cut off of 2.0 *vs* contrast CT[221]. A recent study enrolling 59 PC patients showed similar results, with 91% PPV and 64% NPV for PET-CT. One of the most interesting results was that the clinical management of patients undergoing PET was changed in 16% of cases deemed resectable after routine staging ($P = 0.031$) preventing unnecessary surgery because of distant metastases[222].

Diffuse uptake of FDG is frequent in pancreatitis in comparison to PC (53% *vs* 3%, $P < 0.001$), and therefore PET is extremely useful in distinguishing these two conditions in controversial cases[218,223]. Animal studies have shown that ^{11}C-acetate-PET appears to be superior to FDG PET for the detection of early PC and might be useful in differentiating inflammatory processes from malignancies as ^{11}C-acetate-PET is less affected by the presence of inflammation in human tissues[224].

Another very important characteristic of PET-CT is its ability to provide useful information on tumor viability, and this technique also allows monitoring of tumor response to treatment[217] and the metabolic features of PET help predict the prognosis as a SUV less than 3 appears to be a positive predictive factor[222,225-229].

Similar results were found by Zimny *et al*[230] who showed that better survival trends were noted in patients with PC and a SUV less than 6.0 in comparison to those with a higher SUV. Sensitivity and specificity of imaging modalities are summarized in Table 7.

STAGING

Pathological staging

In the 7th edition of the American Joint Committee on Cancer the different categories of PC are classified according to only one TNM staging system, even if neuroendocrine tumors have a different biology and a better prognosis than ductal carcinomas. Yet, the TNM system provides a reasonable discrimination and prognostic validity for these patients[236].

The TNM system classifies PC into 3 clinically important categories: (1) patients with Tis-T2 PC have localized cancer within the pancreas; (2) patients with T3 cancer have locally invasive disease; and (3) patients with T4 tumors have unresectable PC[237] (Table 8).

Prognostic features of PC include perineural and lymphovascular invasion, elevated serum CA19-9 levels and incomplete tumor resection. Therefore, gross and microscopic assessment of the resection margins is of major importance even if it is not included in the TNM staging system. Patients undergoing resections with grossly or microscopically positive margins have no survival benefits compared to individuals undergoing palliative chemo- radiation therapy alone.

Clinical staging

Surgery is the only chance of cure and the presence of negative resection margins of the primary tumor represent the strongest prognostic factor. Preoperative staging modalities include the combination of several imaging techniques such as CT scan, MRI, EUS, staging laparoscopy and laparoscopic ultrasound which aim to identify patients with resectable disease. There is consensus that patients with distant metastases (liver, lungs, peritoneum)

Table 8 American Joint Committee on Cancer staging of pancreatic cancer

AJCC 6th edition TNM staging system for pancreatic cancer		
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 less in greatest diameter	
T2	Tumor limited to the pancreas, greater than 2 cm at greatest diameter	
T3	Tumor extends beyond pancreas but no involvement of celiac axis or superior mestenteric artery	
T4	Tumor involves the celiac axis or the superior mestenteric artery (unresectable)	
NX	Regional nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
MX	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis	
Stage grouping		
Stage 0	Tis N0 M0	Localized within pancreas
Stage ⅠA	T1 N0 M0	Localized within pancreas
Stage ⅠB	T2 N0 M0	Localized within pancreas
Stage ⅡA	T3 N0 M0	Locally invasive, resectable
Stage ⅡB	T1, 2, or 3 N1 M0	Locally invasive, resectable
Stage Ⅲ	T4 Any N M0	Locally advanced, unresectable
Stage Ⅳ	Any T Any N M1	Distant metastases

AJCC: American Joint Committee on Cancer.

or local invasion of the surrounding organs (stomach, colon, small bowel) are usually not surgical candidates.

The criteria for unresectability of PC include tumor encroachment (defined as tumor surrounding the vessel more than 180 degrees) of arteries such as the celiac artery, hepatic artery, superior mesenteric artery (SMA) or massive venous invasion with thrombosis. Portal or superior mesenteric venous invasion without thrombosis or obliteration of vessels can still be classified as resectable PC[204,238]. A recent study comparing the roles of EUS, CT, MRI and angiography in the assessment of PC staging and resectability has shown that CT scanning was the most accurate in assessing the stage of the tumor (73%), locoregional invasion (74%), vascular involvement (83%), distant metastases (88%), final TNM stage (46%) and overall tumor resectablity (83%)[239]. EUS appeared to be superior in detecting smaller tumors not visualized by CT. A decision analysis demonstrated that the best strategy to assess tumor resectability was based on CT as an initial test and the use of EUS to confirm the results of resectability by CT[221].

Laparoscopic staging

Diagnostic laparoscopy for PC was first introduced as a staging procedure in the late 1980s by Cuschieri *et al*[240] and Warshaw[241,242]. Staging laparoscopy is considered a simple, minimally invasive technique to identify radiographically occult distant metastatic disease and to prevent non-therapeutic laparotomies. Laparoscopic examination allows direct visualization of intra-abdominal contents and has been reported to identify hepatic and peritoneal metastases not shown by other modalities[243] as reported in some studies where 20%-48% of patients considered resectable by CT were found to be unresectable during surgery[244-246].

Diagnostic laparoscopy involves a general exploration of the abdominal surfaces including palpation of the liver with two instruments when necessary. The hilum of the liver is visualized, the foramen of Winslow is examined and periportal lymph nodes are biopsied when enlarged. The transverse colon and omentum are reflected cephalad and the base of the transverse mesocolon is examined with particular attention to the mesocolic vessels. The gastrocolic ligament/omentum is incised and the lesser sac is examined[247].

Laparoscopic ultrasonography (LUS) has been introduced as an additional procedure to increase the detection of intrahepatic metastases, identify enlarged and suspicious lymph nodes and to evaluate local growth in the vascular structures[248]. Some studies have demonstrated that LUS has improved the accuracy of predicting resectability up to 98%[249-251].

Despite these results, the routine use of staging laparoscopy and LUS in patients with radiographically resectable PC remains controversial as imaging modalities have significantly improved, thus reducing the risk of discovering non-resectable disease at the time of surgery. In addition, staging laparoscopy adds costs and it can be time consuming. Sustainers of staging laparoscopy are supported by a study by Kwon *et al*[250], which revealed that staging laparoscopy was able to detect unsuspected metastases and changed the surgical approach in 37% of patients even when using CT, MRI, ERCP and angiography for preoperative staging. Another study by Conlon *et al*[247], supported the use of staging laparoscopy as only 67 out of 115 patients (58%) with PC had resectable disease after completion of the laparoscopic examination. On the other hand, a more recent study from the same group at the Memorial Sloan-Kettering Cancer Center has shown that the yield of staging laparoscopy was only 8.4% when good imaging modalities were obtained at the referral center[252].

Based on the fact that minimally invasive approaches for the diagnosis of PC as well as radiological imaging techniques will continue to advance, the selective use of staging laparoscopy and LUS would play a role in cases where detection of unresectable disease is more likely. Factors which suggest a higher yield with diagnostic laparoscopy include a large primary tumor (diameter larger than 4 cm), a tumor in the body or tail of the pancreas, equivocal findings after imaging tests, severe weight loss, abdominal or back pain, hypoalbuminemia and significantly elevated tumor markers[240].

TREATMENT

Patients with suspected or confirmed diagnosis of PC should be assessed by a multidisciplinary team and stratified as resectable (stage Ⅰ or Ⅱ), borderline resectable (stage Ⅱa or Ⅱb), locally advanced unresectable (stage Ⅲ) or metastatic disease (stage Ⅳ). Treatment should be planned according to local expertise and established guidelines, as resectable and borderline patients should be referred to surgeons, unresectable and metastatic patients should be referred to medical and radiation oncologists and palliative care teams. A multidisciplinary approach to PC is necessary to improve the overall outcome of these patients, especially for borderline resectable or unresectable disease as neo-adjuvant chemo-radiation therapy may play a role in downstaging and the conversion to potentially curable disease[253,254].

SURGICAL THERAPY

Surgical treatment is the only potential cure for PC[255]. Although pancreatic surgery is considered challenging and technically demanding, improvements in surgical techniques and advances in perioperative supportive care have reduced the mortality rates to less than 5% in high-volume centers[256-258]. According to the United States Surveillance and Epidemiology End Results registries, the 5-year relative survival for the period between 1999 and 2006 was 22.5% for localized and 1.9% for metastasizing PC (Table 9)[259].

Because only 20% of patients with PC are candidates for radical resection at the time of diagnosis[260], accurate staging is important in identifying surgical candidates and sparing the risk and cost of surgery for patients who are affected by advanced disease[261]. Unresectable PC is commonly defined when there is tumor invasion of the SMA, inferior vena cava, aorta or celiac arteries; encasement or occlusion of the SMV-portal venous system or by distant metastasis (e.g. hepatic, extra-abdominal, peritoneum, omentum, lymph nodes outside the resection zone)[262]. An Italian study has recently demonstrated that the duration of symptoms (mainly jaundice and celiac pain) of more than 40 d, CA 19-9 levels above 200 U/mL and G3-G4 histological grade of the tumor are poor prognostic parameters, even if the disease is resectable by preoperative staging[263].

Table 9 Stage distribution of pancreatic cancer and 5-year relative survival by stage at diagnosis for 1999-2006, all races and both sexes (SEER registries)

Stage at diagnosis	Stage distribution (%)	5-yr relative survival (%)
Localized (confirmed to primary site)	8	22.5
Regional (spread to regional LNs)	26	8.8
Distant (cancer had metastasized)	53	1.9
Unknown (unstaged)	14	5

SEER: Surveillance Epidemiology and End Results.

Tumor of the head of pancreas

Preoperative biliary decompression *vs* immediate surgical resection: Obstructive jaundice is a common presentation for tumors located in the periampullary area or in the head of the pancreas. To reduce perioperative complications and mortality in patients with obstructive jaundice undergoing pancreaticoduodenectomy (PD), preoperative biliary drainage appears to have a positive impact supported by the findings of several observational studies[264-266]. On the other hand, several other non randomized studies failed to show any advantage of preoperative biliary decompression in these patients, as they developed a higher incidence of bacteriobilia and fungal colonization causing more wound infections, postoperative sepsis and longer hospital stay[267-270]. Two meta-analyses of randomized controlled trials and a systematic review of descriptive series have shown that the outcome of patients undergoing biliary decompression prior to PD was inferior to early surgery as they had higher rates of infectious complications and perioperative mortality[271,272]. These findings were confirmed by a recent multicenter randomized controlled study from the Netherlands which showed that the rates of serious complications were 39% for patients who underwent early surgical resection in comparison to 74% in the group that underwent pre-operative biliary decompression ($P < 0.001$)[264]. Similarly, surgical complications occurred in 37% of patients undergoing early resection in comparison to 47% for individuals who had preoperative biliary decompression. Although the difference did not reach statistical significance ($P = 0.14$), the overall mortality and hospital stay were comparable between the two groups[273].

During the last decade, there has been an increasing interest in treating patients with neo-adjuvant chemoradiotherapy to improve disease-free and overall survival in patients undergoing surgery. Although there are still no phase Ⅲ randomized controlled studies to support the use of this strategy, several phase Ⅱ randomized trials have shown that neo-adjuvant chemo and chemo-radiation therapy are relatively well tolerated, do not reduce the resectability rate and seem to increase the percentage of patients who undergo R0 resections[274-283]. For jaundiced PC patients, candidates for neo-adjuvant therapy must undergo biliary decompression to prevent liver decompensation and stent patency is required for several months. Currently, the only study assessing the outcome

of patients undergoing chemo-radiation therapy prior to PD has shown that plastic stents do not provide patency of the biliary system for long enough to complete the preoperative protocols. In fact, 55% of cases required unplanned repeat ERCP with stent exchange for recurrence of jaundice or ascending cholangitis[284]. For these patients, self expanding metallic stents should be used as the direct costs associated with repeating ERCP and hospital admissions for recurrent biliary obstruction and ascending cholangitis appear to be superior to the initial higher cost of using metallic stents[285].

Standard *vs* pylorus preserving PD: Walter Kausch first described PD in 1912[286], and Allan Whipple later popularized the procedure that bears his name[287]. The classic Whipple (CW) operation consists of an *en-bloc* removal of the pancreatic head, the duodenum, the common bile duct, the gall bladder and the distal portion of the stomach together with the adjacent lymph nodes[288]. This operation can lead to specific long-term complications such as early and late dumping syndrome, post-operative weight loss[289] and post-operative acid and bile reflux[290].

Pylorus preserving PD (PPPD) was first introduced by Watson in 1942[291], and the procedure was popularized by Traverso and Longmire in 1978[292]. Although it was originally described for the treatment of periampullary tumors, many surgeons nowadays perform PPPD for PC in the head of the pancreas. In order to retain a functioning pylorus, the stomach and the first 2 cm of the duodenum are preserved along with their neurovascular supply. The rationale behind preservation of the stomach is to improve long-term gastrointestinal function[293]. There is still some controversy as to which is the best surgical treatment for PC of the head of the pancreas. In comparison to CW, PPPD has the advantages of reduced operative time[294], less blood loss, better access to the biliary anastomosis for post-operative endoscopy in patients with recurrent biliary obstruction, improvement of post-operative weight gain and quality of life[295]. On the other hand, some series have reported that PPPD has a higher incidence of delayed gastric emptying[296,297]. Moreover, it has not been unequivocally shown that PPPD is oncologically equivalent to CW[298]. A number of RCTs and meta-analyses have demonstrated that both perioperative morbidity and long-term outcome are equal in CW and PPPD[263,299,300].

Pancreatic reconstruction: The most significant cause of morbidity and mortality after PD is the development of complications caused by leakage of pancreatic secretions and pancreatic fistulae observed in up to 20% in specialized centers[301,302]. The meticulous reconstruction of pancreatico-enteric continuity is the key to preventing pancreatic fistulae[303]. Pancreatico-jejunostomy and pancreatico-gastrostomy (PG) are the most commonly employed techniques for pancreaticoenteric reconstruction. PG was believed to be an easier technique and less prone to ischemia as a result of the close proximity between the stomach and the pancreatic stump and the presence of a better vascular supply in the stomach in comparison to the jejunum. However, RCTs have not demonstrated superiority of one technique over the other in terms of post-operative complication rates or incidence of pancreatic fistulae[304,305].

Tumor of the body/tail of pancreas

Distal pancreatectomy: Distal pancreatectomy is the surgical procedure of choice for PC of the body and tail of the pancreas. It entails resection of the portion of the pancreas extending to the left of the superior mesenteric vessels and not including the duodenum and the distal bile duct[306]. The spleen is conventionally removed in an *en-bloc* fashion[307]. However, splenic preservation could be accomplished without an increased rate of complications, operative time or the duration of post-operative hospital stay[295,308]. Several closure techniques have been introduced for the pancreatic remnant in an attempt to reduce pancreatic fistulae. They include hand-sewn suture techniques, staple closure techniques or a combination of both[309-312], ultrasonic dissection devices[313], pancreatico-enteric anastomosis[314], application of meshes, seromuscular[315] and gastric serosal patches[316], or sealing the pancreatic stump with fibrin glue[199].

Cancers of the body and tail of pancreas usually present at a later stage of the disease in comparison to PC of the head due to lack of early symptoms[317]. There are no survival differences between resections for equal TNM stage tumors of the head *vs* tumors of the body and tail as shown by a retrospective study that reported a 5-year survival of 17% after resection of the pancreatic head *vs* 15% for left-sided tumors in stage I cancers[318].

Laparoscopic pancreatic resection: Laparoscopic pancreatic surgery represents one of the most challenging abdominal operations[319,320]. Gagner and Pomp were the first to describe a laparoscopic duodeno-pancreatectomy in 1994[321]. Since then, the total number of laparoscopic duodeno-pancreatectomies has remained small due to technical difficulties associated with this operation[322]. A recent study from the Mayo clinic with 65 patients who underwent total laparoscopic PD (TLPD) outlined that TLPD is safe, feasible and its results appear to be comparable to the open approach[323] (Table 10).

Nevertheless, larger prospective studies are required in order to better assess the advantages of TLPD.

Laparoscopic distal pancreatic resection is currently the most frequently performed laparoscopic pancreatic surgery[327]. Most of the studies on distal laparoscopic pancreatectomy are case series with a relatively small number of patients[328]. Although recent studies have shown that laparoscopic distal pancreatectomy is feasible and safe[329-331], the morbidity, mortality and hospital stay are similar to those after open surgery[332]. This is probably due to the fact that morbidity after pancreatic surgery results from retroperitoneal dissection, length of the operation and pancreatic fistulae rather than the incision. In addition, a recent prospective observational study comparing 85 open *vs* 27 laparoscopic distal pancreatectomies has shown

Table 10 Published results on laparoscopic pancreaticoduodenectomies

Author	Yr	Patient No.	Morbidity (%)	Pancreatic fistula (%)	Mean hospital stay	Mortality (%)
Kendrick *et al*[323]	2010	62	42	18	7	1.6
Palanivelu *et al*[324]	2007	42	28.6	7.1	10.2	2.4
Dulucq *et al*[325]	2006	25	31.8	4.5	16.2	0
Pugliese *et al*[326]	2008	19	31.6	15.8	18	0

that the number of lymph nodes removed during the minimally invasive procedure was significantly inferior (mean number: 5.2) in comparison to the open approach (mean number: 9.4)[333]. These findings suggest that at this time there is a lack of evidence to support oncological equipoise between laparoscopic and open resections for PC.

Total pancreatectomy: Total pancreatectomy has been employed in selected patients with chronic pancreatitis[334], multifocal islet cell tumors or diffuse IPMN[335]. Total pancreatectomy for PC was initially proposed to avoid the risk of pancreatico-enteric leaks and to remove potential undetectable synchronous disease in other parts of the gland[336]. However, the indication of total pancreatectomy to avoid the risks of pancreatic fistulae is still controversial[337]. Improvement in operative techniques, advances in nutritional support, critical care and interventional radiology have significantly decreased the incidence of life-threatening sequels of pancreaticoenteric leaks[338]. In addition, the permanent endocrine insufficiency associated with total pancreatectomy impacts enormously on the quality of life and long-term outcome of these patients[339]. Some studies have demonstrated a significant increased risk of perioperative morbidity and mortality associated with total pancreatectomy compared with PD[318]. A recent study by Reddy *et al*[335] showed that long-term survival rates were equivalent after total pancreatectomy and PD (19.9% *vs* 18.5%), supporting the fact that there is no oncological benefit of total pancreatectomy *vs* a more limited resection in PC. Currently, total pancreatectomy should be performed in patients with PC if it is the only oncologically sound treatment option[335].

Vascular resections and extended lymphadenectomy: With the advancement in operative techniques and perioperative management of patients with PC, more radical surgical procedures with vascular resection and extended lymphadenectomy have been proposed for selected cases[340]. The results of extended vascular and lymphatic resections remain controversial.

The principal use of venous resection and reconstruction is to allow complete tumor clearance when precluded by tumor involvement of the superior mesenteric or portal vein, and when the surgeon expects to achieve a negative resection margin[341]. Post-operative morbidity and mortality rates following portal or superior mesenteric vein resections seem to be similar to those of patients with standard PD (42%-48.4% *vs* 47.1%, 3.2%-5.9% *vs* 2.5%, respectively)[342,343]. Another study showed that patients undergoing pancreatic resection with venous reconstruction (VR) had a median survival of 22 mo compared to 20 mo for those who had classic PD ($P = 0.25$)[344]. In another study, a slight survival benefit was noted in patients who did not require VR (33.5%) compared to those with VR (20%, $P = 0.18$), although this did not reach statistical significance[345].

Pancreatectomies with major arterial resections (common hepatic artery/celiac axis and superior mesenteric artery) have been reported in recent years with acceptable outcomes. Nevertheless, arterial reconstruction during pancreatectomies remains a challenging procedure with increased risk of complications compared to classic PD and PD with VR. In addition, most PCs with arterial invasion are for the majority, advanced tumors with distant lymph node involvement and metastases, and therefore indicated only in a very select group of patients[346]. Recent data on pancreatectomies requiring arterial resections at high volume tertiary centers have shown operative mortality rates of 4.3%[346], peri-operative mortality rates (60 d) of 17%[347], morbidity rates of 48%[348] and 3-year survival rates of 17%-23.1%, which are much higher than for classic PD[346,347].

It has been noted that lymph node involvement outside the standard PD specimens occurs in more than 30% of cases[349]. This has led to the evaluation of the need for a more extended lymph node dissection (ELND) in the surgical management of PC. To date, the definitions of a standard lymphadenectomy as well as ELND are still not very clear[341]. A number of Japanese studies have shown an increased survival rate in patients who have undergone ELND compared to conventional PD[350-352]. However, these studies were not randomized and their data were not validated by other centers[353].

The first RCT comparing standard PD and ELND was reported by Pedrazzoli *et al*[354] in 1998. In this study, standard lymph node dissection was defined as the removal of lymph nodes from the anterior and posterior pancreatoduodenal region, pyloric region, biliary duct, superior and inferior pancreatic head and body. In addition to the above, ELND included removal of lymph nodes from the hepatic hilum and along the aorta from the diaphragmatic hiatus to the inferior mesenteric artery and laterally to both renal hila, with circumferential clearance of the origin of the celiac trunk and SMA. This study showed no difference in morbidity, mortality or 4-year survival rates between the two groups.

Recently, a meta-analysis on standard PD and PD + ELND for PC patients showed comparable morbidity and mortality rates with a trend towards higher rates of delayed gastric emptying in the ELND group. The weighted

Table 11 Survival data after resection of pancreatic cancer

Author	Yr	Resection (*n*)	R0 resection (*n*)	Overall 5-yr survival (%)	R0 5-yr survival (%)	Median survival (mo)
Fatima *et al*[371]	2010	617	468	17.4	20	18
Kato *et al*[376]	2009	138	115	9.9	13.2	12.3
Raut *et al*[373]	2007	360	300	NA	NA	24.9
Cameron *et al*[258]	2006	1000	NA	18	23	33
Shimada *et al*[372]	2006	88	66	19	26	22
Howard *et al*[375]	2006	126	158	4	67	18
Moon *et al*[374]	2003	81	20	10.8	67.8	11.8

NA: Not applicable.

mean log hazard ratio for overall survival was 0.93 (CI: 0.77-1.13), revealing no significant outcome differences between the standard and extended procedure ($P = 0.480$) suggesting that ELND does not benefit overall survival and has a trend towards increased morbidity[355].

CLINICAL VOLUME AND OUTCOMES

During the last two decades, several large observational studies in the U.S., Canada and the Netherlands have shown that the institutional volume of pancreatic resections affects patients' outcomes. Higher perioperative morbidity, mortality and decreased use of multimodality therapy have been observed more frequently in low volume centers[356-363]. In 1993, Edge and colleagues reported that case load did not correlate with mortality after pancreatic resection[364]. However, surgeons who performed fewer than 4 resections per year had more complications. Recent studies have shown significant improvements in perioperative morbidity and mortality in patients undergoing pancreatic resections in high volume centers. For example, investigators at Memorial Sloan Kettering Cancer Center found that in a cohort of 1972 patients, high-volume centers defined as performing more than 40 cases per year in New York State had significantly less mortality (4% *vs* 12.3%) than low volume centers[356].

The definition of high and low volume varied among all these studies, but the findings were consistent and were confirmed by Birkmeyer *et al*[365] who showed that very low volume centers (0-1 procedure per year), low volume hospitals (1-2 procedures per year) and higher volume hospitals (more than 5 procedures per year) had significantly different mortality rates (16% and 12% *vs* 4% respectively; $P < 0.001$). The largest difference in operative mortality between very low volume (17.6%) and high volume (3.8%) centers is even more significant for PD when compared to other major surgeries as shown in a retrospective analysis of data from the national Medicare claims database and the Nationwide Inpatient Sample[257].

A recent study involving 301 033 patients with PC included in the National Cancer Database evaluated the treatment patterns of 1667 hospitals over a 19-year period[366]. During that time the pancreatectomy rate as well as the use of multimodality adjuvant therapy for patients with stage I and II disease increased significantly (pancreatectomy rate increased from 39.6% to 49.3%; $P < 0.001$, and the use of multimodality therapy increased from 26.8% to 38.7%; $P < 0.001$). Furthermore, patients were more likely to receive multimodality therapy at academic institutions, particularly those considered to be high volume hospitals. Despite these important advances, it appears that there is still a high percentage (71.4%) of patients with potentially resectable disease who are still not referred for surgical therapy as reported by Bilimoria *et al*[367]. These findings would suggest that a persistent nihilism of clinicians towards PC amd pancreatectomy may be the most significant correctable factor that contributes to the current poor long-term outcomes of PC.

ADJUVANT CHEMORADIATION THERAPY

Several single agent chemotherapeutic agents have been tried in the treatment of PC. 5-FU has been used in PC for more than 25 years with response rates of 8%-15%[368]. The addition of Leucovorin to 5-FU doubled the response rate to 26%, however, it showed no benefit in terms of survival[369]. The only chemotherapeutic agent that demonstrated prolonged survival in comparison to 5-FU and Leucovorin was Gemcitabine[370].

After pancreatic resection, the 5 year survival rate is only 20% or less as PC has a high loco-regional recurrence rate and a tendency towards early liver metastasis (Table 11)[258,371-376].

Based on these observations it appears necessary to employ adjuvant therapy in combination with surgical resection in order to improve survival. Only a few years ago there was no valid data on adjuvant chemoradiation therapy after curative surgical resection[377].

The first RCT that showed benefit from adjuvant chemoradiation therapy in comparison to surgery alone was the Gastrointestinal Tumor Study Group (GITSG) trial, where patients receiving 40 cGy followed by 5-FU showed a mean survival of 18 mo in comparison to 11 mo for those who received surgery alone ($P = 0.05$). The two- and five-year survival rates of the two groups were 43% *vs* 18% and 19% *vs* 0%, respectively[378].

The EORTC (European Organization for Research and Treatment of Cancer) study showed that patients undergoing chemoradiation therapy (5-FU protocol) had a median survival of 17.1 mo compared to 12.6 mo for the

controls (P = 0.099). The two- and five-year overall survival rates were 37% and 20% for the experimental arm and 23% and 10% for the control arm (P = NS)[379].

The European Study Group for PC 1 trial (ESPAC-1) compared four groups of patients who underwent pancreatic resection; (1) surgery alone; (2) 5-FU and Leucovorin adjuvant chemotherapy; (3) combination of adjuvant radiation therapy and 5-FU chemotherapy; and (4) adjuvant chemoradiation followed by chemotherapy[380]. In this study, the five-year survival rate for patients who received adjuvant chemotherapy was 21% compared to 8% for patients who did not (P = 0.009). Patients who underwent chemoradiation therapy had an inferior five-year survival rate (10% *vs* 20%) in comparison to patients who did not receive radiation (P = 0.05).

In 2006, the Radiation Therapy Oncology Group trial compared patients receiving adjuvant chemoradiation (5040 cGy in combination with continuous 5-FU) followed by 5-FU *vs* similar chemoradiation therapy followed by Gemcitabine. For patients affected by PC of the head, the arm treated with Gemcitabine had a superior median (18.8 mo *vs* 16.7 mo) and overall survival at 3 years [31% *vs* 21% (P = 0.047)], but with a higher incidence of toxicity (80% *vs* 60%)[381].

In 2007, a RCT conducted in Germany and Austria (CONKO-1 [Charite Onkologie Clinical Studies in GI Cancer 001]) compared patients undergoing R0 or R1 pancreatic resection alone *vs* resection followed by Gemcitabine-based chemotherapy. The median disease-free survival for patients treated with Gemcitabine was 13.9 mo *vs* 6.9 mo in the observation arm (P < 0.001), although there was no difference in the overall survival between the two groups (22 mo *vs* 20 mo)[382]. From the results of these studies, adjuvant chemotherapy has become the standard of care for patients who can tolerate the treatment after surgical resection.

NEOADJUVANT THERAPY

Neoadjuvant therapy is defined as the preoperative intervention aiming to convert unresectable PCs to resectable tumors or to increase the probability of complete microscopic tumor resection[383]. One of the limitations of the role of neoadjuvant therapy for PC is the fact that there is no standardized definition for tumor resectability and there is no data from randomized phase three trials on the benefit of neoadjuvant therapy. In addition, data from prospective and retrospective studies have several biases due to heterogeneity of inclusion and exclusion criteria, preoperative quality of imaging tests, and surgical pathology reports on lymph node involvement and resection margin status.

A recent systematic review[383] evaluating retrospective and prospective studies on neoadjuvant chemo and radiation therapy from 1966 to 2009 included a total of 111 studies and 4,394 patients. The results of this meta-analysis showed that the majority of patients were treated with Gemcitabine, 5-FU or oral analogue Mitomycin-c, and Platinum compounds. Patients undergoing neoadjuvant treatment received radiotherapy in the range of 24-63 Gy. The analysis showed that neoadjuvant treatment in patients with unresectable tumor was able to convert 33.2% of patients to resectable candidates, providing a median survival of 20.5 mo which was equivalent to patients undergoing resection followed by adjuvant therapy who had median survival of 20.1 to 23.6 mo. On the other hand, neoadjuvant therapy for patients with resectable cancer did not seem to improve overall outcome.

RADIATION THERAPY

Persistent loco-regional disease after pancreatic surgery is a major determinant of recurrence[384]. Although there is supportive evidence for the use of adjuvant chemotherapy[380,385], the role of adjuvant radiation remains unresolved. Generally it is believed that external-beam radiotherapy (EBRT) alone is a suboptimal treatment for locally advanced PC as most patients will die of systemic disease[386].

In the Mayo clinic clinical trial and the GITSG trial, patients who were randomized to receive EBRT only had a median survival of 5.3-6.3 mo which was inferior to EBRT plus 5-FU[387,388].

Among 210 patients who underwent surgical resection for PC [PD (73%), total and/or distal pancreatectomy (25%), Appleby procedure (2%)] followed by intraoperative electron beam radiotherapy (IOERT), some patients received a single fraction of IOERT alone (25 Gy), whereas others (30%) received additional EBRT and 54% received various forms of adjuvant chemotherapy. The study demonstrated excellent local control with the addition of IOERT (75%). Despite the benefit in local control, the overall median survival was similar to other studies with adjuvant chemotherapy or chemoradiation (19 mo)[389]. A combined study of extended resection and intraoperative radiation therapy (IORT) concluded that IORT contributed to local control; however, it provided no overall survival benefits (14.6% 5-year survival)[390].

In the United States, chemoradiation with concurrent 5-FU followed by Gemcitabine continues to represent the standard for adjuvant therapy of tumor of the pancreatic head. A direct comparison of chemo-radiation therapy and chemotherapy alone seems to be difficult to achieve and additive chemotherapy before or after chemo-radiation-therapy will have to be tested in randomized studies in order to determine the optimal sequencing[391].

PALLIATIVE MEASURES

Palliative treatment of patients with PC plays a very important role as 80% to 90% of newly diagnosed tumors are not resectable due to local invasion or presence of distal metastatic disease[392]. Median survival for patients with unresectable PC located in the head and body of the gland is approximately 7 mo, while for PC located in the tail median survival is significantly less [3 mo (P = 0.0002)], as they are usually diagnosed in more advanced stages[393]. For these patients, relief of symptoms secondary to gastric outlet obstruction, jaundice and pain are essential to

improve their quality of life and overall survival. In the past, surgical palliation was more common as the diagnosis of unresectable disease was frequently done in the operating room and patients underwent one or more of the following procedures: gastric bypass, hepatico-enteric decompression and celiac plexus neurolysis for pain relief during the same surgery. With the improvement in diagnostic imaging tests, the role of surgical staging has decreased as the vast majority of patients can be currently classified as suffering from unresectable disease by non-invasive modalities such as CT and MRI or by endoscopic US. Nevertheless, there are still controversies on the best palliative strategies for these patients as there is a lack of randomized controlled trials and abundant contrasting data from observational studies.

Gastro-duodenal decompression

There is still some controversy on the use of routine gastro-intestinal bypass for PC diagnosed as unresectable at the time of exploratory laparoscopy or laparotomy.

In a large observational study of 155 patients with unresectable PC staged by extended laparoscopy at the Memorial Sloan Kettering Cancer Center, only 4% of patients required surgical intervention for gastric outlet obstruction before their death: 2 patients required open gastro-jejunal anastomosis alone and 1 patient underwent a combined gastro and hepatico-jejunostomy a few days after laparoscopy[393]. In addition, 1 patient required a percutaneous endoscopic gastrostomy for palliation of gastric outlet obstruction a few weeks before demise. The authors concluded that the routine use of gastric bypass in patients with unresectable PC is not indicated. On the other hand, several other retrospective studies[394,395] have suggested that up to 25% of patients with unresectable PC would develop gastric outlet obstruction requiring surgical intervention.

A recent prospective randomized trial compared 44 patients who were found unresectable at the time of surgery and who underwent a retrocolic gastro-jejunostomy to 43 patients who did not[396]. The two groups had similar morbidity (32% *vs* 33%), mortality (0%) and hospital stay. On the other hand, patients who had gastric bypass did not develop any gastric outlet obstruction, while 19% of patients in the control group did ($P < 0.01$). Although this study would suggest that gastric bypass should be performed in all patients found unresectable at the time of surgery, the introduction of metallic self-expanding intestinal stents has changed the options for palliation.

A prospective multicenter cohort study of 51 patients with malignant gastric outlet obstruction treated with self-expandable metallic stents showed that in 98% of cases the stent was successfully deployed and that the median duration of patency was 10 mo. Only 14% of patients had stent dysfunction, and migration was observed in only 2% of cases[397]. Similar results were reported by another study from South Korea which showed a median stent patency of 385 d, and only 1% serious complications (gastrointestinal bleeding or perforation)[398]. Other observational studies have shown that compared with palliative surgery, stent placement provides a shorter hospital stay, earlier resumption of oral intake, fewer complications and lower hospital costs[399,400]. The only randomized controlled study that compared duodenal stent and laparoscopic gastrojejunostomy favored endoscopic therapy as it was associated with less discomfort, shorter hospital stay and improved physical health scores at 1 mo[401]. In this small study, only a third of patients were alive at 1 year and no cases of stent occlusion were observed. The two groups had similar overall survival supporting equipoise between endoscopic and surgical palliation. Nevertheless, surgical palliation can still play an important role when patients have a long life-expectancy, need biliary and gastric bypass in combination with celiac neurolysis for pain control.

Biliary decompression

The majority of PCs occur in the head of the pancreas and obstructive jaundice is one of the early symptoms for 50%-80% of patients[396]. In the past, staging laparotomy and biliary bypass were frequently performed for unresectable PC of the head[402,403]. During the last decades, the development of interventional radiology and endoscopy has allowed palliation of obstructive jaundice by the insertion of percutaneous or endoluminal stents with minimal morbidity and mortality. Currently, endoscopic biliary stenting is the treatment of choice for unresectable PC with obstructive jaundice. Percutaneous transhepatic stenting is reserved only for patients in whom endoscopic stenting has failed as it is associated with a higher complication rate than endoscopic palliation (61% *vs* 35%)[404,405]. High risk surgical patients are best managed by biliary stenting, however, it is still unclear whether palliative surgical biliary decompression is superior to other interventions for patients who are fit for surgery or who have a longer life expectancy. A European randomized controlled study comparing surgical biliary decompression *vs* endoscopic plastic stenting showed that both interventions were equally successful in palliating jaundice (95% *vs* 94%, respectively) and provided equal overall survival. Nevertheless, major complications (29% *vs* 11%) and procedure-related mortality (14% *vs* 3%) were significantly higher for surgical patients[406]. In addition, surgical decompression was more expensive than stenting, although recurrent biliary obstructions and late gastric bypasses were more common in patients undergoing endoscopic treatment even if that did not reach statistical significance. Similar results were reported in a more recent Brazilian study which found that endoscopic therapy with self-expandable metallic stents was more cost-effective than surgical decompression (US$2832 *vs* US$3821, $P = 0.031$) and provided better quality of life at 30 ($P = 0.04$) and 60 d ($P = 0.05$)[407]. The only available meta-analysis of randomized controlled studies comparing surgery with endoscopic stenting included only 3 studies where none tested the use of metallic self-expanding stents[408]. Although the reintervention rate was 3% (0%-16%) in surgically treated patients compared with 36% (28%-43%) in stented patients, because of the limited number of studies with a relatively small group of patients and heterogeneous quality, the authors

concluded that they could not identify which treatment was preferable.

The patency of biliary stents has greatly improved with the introduction of expandable metallic stents (EMS) as they offer a larger diameter for drainage and are associated with a lower occlusion rate than plastic stents[409,410]. The concurrent use of chemotherapeutic agents in patients palliated with SEMS was thought to increase the risk for ascending cholangitis. However, a Japanese retrospective study has demonstrated that the combination of SEMS and palliative chemotherapy for unresectable PC did not change the incidence of biliary infectious complications[411]. In patients with combined biliary and duodenal obstructions, concomitant biliary and duodenal stenting is now feasible and justified as the need to repeat endoscopic therapies is rarely required even in long-term survival patients[412].

Currently, surgical biliary bypass is advocated only for patients with obstructive jaundice who fail endoscopic or percutaneous stent placement.

Pain control

About 70% of patients with unresectable PC develop clinically important pain during their lives[413]. Pain is the main cause of the significant drop in quality and quantity of life of these patients and good palliation is necessary as pain incidence and severity increases with disease progression[414].

For the majority of patients, pain from PC can be managed with opioid analgesics. However, approximately one third of patients experience inadequate control of pain with oral analgesics alone[415]. For these patients, radiation therapy, chemotherapy and celiac plexus neurolysis have been used. Percutaneous neurolytic celiac plexus block with injection of 50%-100% ethyl alcohol under radiological guidance has become the most commonly recognized method of splanchnicectomy with a 70%-96% success rate[416]. The celiac plexus block has several advantages as it has been proven to ease pain without the side effects of opioids and can be administered intraoperatively, percutaneously, or by endoscopic ultrasonography. Recent studies have shown that endoscopic ultrasonography-guided neurolysis is effective and has minimal risk of the potentially serious complications associated with surgical or percutaneous approaches[417,418].

A recent double-blind randomized controlled study comparing patients treated with celiac plexus block *vs* systemic analgesic therapy showed that splanchnic neurolysis provided superior pain relief and quality of life scores, but overall opioid consumption, frequency of opioid adverse effects and overall survival did not reach statistical significance between the two groups[419]. For the majority of PC patients, pain is still controlled pharmacologically even if other modalities such as surgical thoracoscopic splanchnicectomy, epidural anesthesia, subcutaneous injection with octreotide, hypofractionated-accelerated radiotherapy and more recently photodynamic therapy have shown some temporary success[414,420-423].

Nutritional supportive care

The median survival of patients with unresectable PC is 33 wk and for advanced metastatic disease is only 10 wk[424]. About 90% of patients with PC have significant weight loss at the time of diagnosis and all of them develop progressive cachexia due to neoplastic metabolic derangements. Secondary events such as pancreatic exocrine insufficiency due to pancreatic duct obstruction, fat malabsorption due to biliary obstruction and poor oral caloric intake caused by nausea or gastric outlet obstruction are also responsible for the progressive weight loss. Even if weight loss has been found to have a prognostic effect on survival, most of the palliative care interventions for PC are directed at correcting biliary obstruction, gastric outlet obstruction and pain, and relatively little attention has been paid to interventions that can prevent or reduce the progressive weight loss of these patients[425]. Recently, a placebo-controlled trial comparing patients receiving enteric coated pancreatic enzyme supplements *vs* placebo showed that after 2 mo, patients receiving pancreatin had gained 1.2% of their body weight in comparison to controls who lost 3.7% ($P = 0.02$), and that they had higher daily total energy intake (8.4 MJ *vs* 6.6 MJ, $P = 0.04$)[424]. Although the Karnofsky performance status between the two groups was not different and survival analysis was not performed to determine if body weight gain translates into better prognosis, this study was the first to show an effective palliative strategy able to increase the intestinal absorptive function of patients who suffer from steatorrhea.

CONCLUSION

In recent decades, diagnostic modalities, and the surgical and palliative treatments of PC have clearly progressed although the overall prognosis has barely changed. The management of patients affected by PC is complex and requires expertise in many fields. Multidisciplinary teams are necessary to optimize the overall care, and palliative techniques have to be mastered as the majority of PCs are diagnosed in advanced stages. Better outcomes are reached if PC patients are appropriately referred to tertiary centers for assessment by surgical, medical and radiation oncologists, gastroenterologists, palliative care specialists and other dedicated health care providers. Despite recent progress, there is still a very limited ability to detect PC at an early stage, and there is a need for more studies to better understand genetic predisposing factors and to discover new markers that could assist physicians in this task. Randomized controlled studies are necessary to explore the role of neo-adjuvant therapies and new protocols for adjuvant strategies in patients undergoing pancreatic resection.

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