Journal of Gastrointestinal & Digestive System

Malhotra et al., J Gastrointest Dig Syst 2015, 5:2
DOI: 10.4172/2161-069X.1000278

Review Article Open Access

The Pathogenesis, Diagnosis, and Management of Pancreatic Cancer

Lavina Malhotra, Daniel H. Ahn and Mark Bloomston*

Division of Surgical Oncology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA

***Corresponding author:** Mark Bloomston, MD, Associate Professor of Surgery, Division of Surgical Oncology, The Ohio State University Wexner Medical Center, N924 Doan Hall, 410 W. 10th Avenue, Columbus, Ohio 43210, USA, Tel: 614-293-4583; Fax: 614-366-0003; E-mail: Mark.bloomston@osumc.edu

Rec date: Mar 3, 2015, **Acc date:** Apr 9, 2015, **Pub date:** Apr 15, 2015

Copyright: © 2015 Malhotra L, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

Abstract

Pancreatic cancer is an aggressive and devastating disease accounting for 44,000 new cases per year in US. It is characterized by invasiveness, rapid progression and profound resistance to treatment. The majority of cases are diagnosed above age 65 with about 60% of cases at an advanced stage and 5 year survival less than 10%. Advances in molecular biology have greatly improved our understanding of pathogenesis of pancreatic cancer. Many patients have mutations of K-ras oncogene and various tumor suppressor genes are also investigated. Radical surgery remains the only curative treatment option for pancreatic cancer in early stages. For locally advanced, unresectable and metastatic disease, treatment is palliative, in form of adjuvant or neoadjuvant chemotherapy with or without radiotherapy. Gemcitabine based combinations have essentially failed to provide a substantial prolongation of survival and constitute treatment option only in patients with a good performance status. This article provides an overview of epidemiology; risks factors, molecular genetics, biomarkers, diagnostic modality and evidence based therapeutic options for resectable and palliative options for unresectable disease.

Keywords: Pancreatic cancer; Diagnosis

Epidemiology

Pancreatic cancer is one of the most lethal human cancers and is the fourth leading cause of cancer-related deaths in the United States [1,2]. It is estimated that 38,460 of 45,220 people diagnosed with pancreatic cancer in the United States in 2013 will die of their disease, representing approximately 6% of total U.S. cancer deaths [1]. Typically a cancer of the elderly, only 13% of cases occur in patients younger than 55 years, whereas 69% of cases occur in those older than 65. There is a slight predilection for men over women in most countries. Furthermore the incidence of pancreatic cancer in the United States increased from 1999 to 2008, possibly because of the increasing prevalence of obesity and other unknown factors [1,3-5]. Mortality rates have remained largely unchanged [6].

The etiology of pancreatic cancer remains unclear, thus making specific risk factors allusive. Still, accepted associated risk factors include smoking, family history of chronic pancreatitis, advancing age, male gender, diabetes mellitus, obesity, non-O blood group, occupational exposures (to chlorinated hydrocarbon solvents and nickel), African American ethnic origin, a high-fat diet, diets high in meat and low in vegetables and folate, and possibly Helicobacter pylori infection and periodontal disease [7]. Findings of preliminary studies suggest that metformin could protect against development of pancreatic cancer [8,9]. A retrospective analysis of 302 patients with pancreatic cancer and diabetes found that metformin use was associated with increased survival at 2 years (30.1% vs. 15.4%; P=0.004) and increased overall survival (OS) (15.2 months vs. 11.1; P=0.009). The OS difference was significant only in patients without distant metastases and remained significant when insulin users were excluded [10]. Although the cause of pancreatic cancer is complex and multi factorial, cigarette smoking and family history are dominant. About 20% of pancreatic cancers are associated with cigarette smoking and cancers in smokers harbor more genetic mutations than those in non-smokers [11]. A family history of pancreatic cancer is an important risk factor for disease with 7-10% of affected individuals having a family history [12]. True familial pancreatic cancer is rare; however, a genetic predisposition may be present in up to 5-10% and familial excess of pancreatic cancer is associated with high risk. Prospective analysis of afflicted families has shown that first degree relatives of individuals with familial pancreatic cancer have a nine fold increased risk over the general population. A variety of syndromes are also associated with an increased risk of pancreatic cancer. Individuals who are carriers of the germline BRCA2 mutation have up to a 10-fold greater risk of developing pancreatic cancer over the general population. Other syndromes, and their associated genetic alteration, include hereditary pancreatitis, hereditary nonpolyposis colorectal cancer—the Lynch II variant (hMSH2, hMLH1) [13], familial atypical multiple mole melanoma (FAMMM) syndrome (p16) [14], Peutz-Jeghers syndrome (STK11/LKB1), and ataxia telangiectasia (ATM). Germline mutations in the STK11 gene [15] result in Peutz-Jeghers syndrome, in which individuals have gastrointestinal polyps and an elevated risk for colorectal cancer. These individuals also have a highly elevated risk for developing pancreatic cancer. Lynch syndrome is the most common form of genetically determined colon cancer predisposition and is caused by germline mutations in DNA mismatch repairgenes (MLH1, MSH2, MSH6, or PMS2) [15]. Patients with Lynch syndrome also have an elevated risk for pancreatic cancer. BRCA2 gene testing should be considered after appropriate genetic counseling for patients of Jewish ethnic origin, those with a strong family history of breast cancer, or individuals with two or more first degree relatives with pancreatic cancer [16]. Germline CDKN2A [14] testing should be considered if those with a family history of familial atypical multiple mole melanoma [17].

Molecular Genetics

The genes involved in the pathogenesis of pancreatic cancer can be divided into three categories: tumor-suppressor genes [18], oncogenes

[19], and DNA mismatch-repair genes [20]. Understanding these mutations is critical to a better understanding of familial pancreatic cancer and to the development of gene-based screening tests and therapies. The most frequent genetic abnormalities in invasive pancreatic adenocarcinoma are mutational activation of Kras oncogene [21], inactivation of tumor suppressor genes including CDKN2A [22], TP53, SMAD4, and BRCA2, widespread chromosomal losses, gene amplifications, and telomere shortening. Kras mutations and telomere shortening are the earliest known genetic abnormalities recorded, even in low grade pancreatic intraepithelial neoplasias (PanIN) [23]. Telomere shortening is believed to contribute to chromosomal instability, whereas inactivation of TP53, SMAD4, and BRCA2 happens in advanced PanINs and invasive carcinomas. Genes mutated in a few (<20%) pancreatic cancers include oncogenes [24] such as BRAF, MYB, AKT2, and EGFR, and tumor suppressor genes [18] such as MAP2K4, STK11, TGFBR1, TGFBR2, ACVR1B, ACVR2A, FBXW7, and EP300. Structural analysis of mutated genes implicates PIK3CG, DGKA, STK33, TTK, and PRKCG as low-frequency driver mutations [22].

In addition to the driver genes, epigenetic changes can also alter gene function in pancreatic cancers. Epigenetic dysregulation includes alterations in DNA methylation [18] and histone modifications and non-coding RNAs [25]. Promoter methylation and gene silencing in pancreatic cancers was first reported for the tumor suppressor gene CDKN2A [17], of which epigenetic silencing is restricted to neoplasms without genetic inactivation of CDKN2A [17]. Only a few classic tumor suppressor and DNA repair genes undergo epigenetic silencing in pancreatic cancers: MLH1 and CDH1 are methylated in a small proportion of tumors. Many other genes are frequent targets of aberrant methylation [18] and gene silencing in pancreatic cancers [26] including CDKN1C, RELN, SPARC, TFPI2, and others. Some of the most common aberrantly hypermethylated genes in pancreatic neoplasms have been evaluated for their diagnostic or biological relevance. Promoter hypomethylation of overexpressed genes has also been reported for several genes, such as SFN, MSLN, and S100A4 and mucin genes [27]. Alterations in microRNA expression seem to contribute to cancer development and progression. Overexpression of several microRNAs in pancreatic cancers including miR-21, miR-34, miR-155, and miR-200 is thought to contribute to neoplastic progression [28]. Furthermore, since microRNAs are stable and detectable in human plasma they could be useful diagnostic markers. Genetic and epigenetic alterations of pancreatic cancers probably play a part in tumor aggressiveness and patterns of progression [29]. Tumor-stromal interactions contribute to oncogenic signaling, including interactions entailing the hedgehog pathway, cyclo-oxygenases, the extracellular matrix protein SPARC, and NFκB, among others [30]. Hedgehog ligands derived from pancreatic cancer cells stimulate non-neoplastic stromal fibroblasts that over express the hedgehog pathway receptor called smoothened (SMO), and this paracrine hedgehog signaling stimulates fibroblast-mediated tumor growth; this mechanism of activation of the hedgehog pathway is more typical than alterations of the hedgehog pathway in pancreatic cancer cells [20]. Targeting of the hedgehog pathway has recently been a treatment strategy in clinical trials for pancreatic cancer with mixed results [30].

Pathophysiology

The most common neoplasms of the exocrine pancreas are the ductal adenocarcinomas based on their cell of origin.

Solid epithelial tumors

Ductal adenocarcinoma account for three-fourths of all malignant pancreatic neoplasms [31]. Grossly these tend to be white-yellow, poorly defined hard masses that often obstruct the distal common bile duct and/or main pancreatic duct. Microscopically they contain infiltrating glands of varying size and shape surrounded by dense reactive fibrous tissue. The nuclei of the cells show marked pleomorphism, hyperchromasia, loss of polarity and prominent nucleoli with the epithelial cells often containing mucin [32]. Ductal adenocarcinomas tend to infiltrate into perineural, lymphatic, and vascular spaces and frequently tend to metastasize early to liver (80%), peritoneum (60%), lungs and pleurae (50% to 70%) and adrenal glands (25%) [23]. Much like colon cancer, pancreatic cancer also tends to demonstrate a step-wise progression to a malignant phenotype from benign precursor lesions [20]. These precursor lesions are referred to as pancreatic intraepithelial neoplasia (PanIN). PanINs are lesions composed of mucin-producing epithelia with varying degrees of cytologic and architectural atypia that involve the small ducts of the pancreas [33]. PanINs can be flat (PanIN-1A), papillary without atypia (PanIN-1B), papillary with atypia (PanIN-2), or may even meet histopathologic criteria for carcinoma in situ (PanIN-3) [33]. PanIN-3 is associated with severe architectural and cytonuclear abnormalities, but invasion through the basement membrane is absent. Just as there is progression from adenoma to adenoma with high-grade dysplasia to infiltrating adenocarcinoma in the colon, so too is there progression from PanIN-1 to PanIN-2 to PanIN-3 to infiltrating adenocarcinoma in the pancreas. Several lines of evidence suggest that PanINs are precursors of infiltrating pancreatic cancer: PanINs are often found in association with ductal adenocarcinomas, three-dimensional mapping techniques have demonstrated a stepwise transformation from mild dysplasia to severe dysplasia in pancreatic duct lesions. PanINs demonstrate some of the same genetic changes seen in infiltrating adenocarcinomas, most notably activating point mutations in codon 12 of the K-ras gene, and also harbor mutations in tumor-suppressor genes, namely p16, p53, BRCA2, and DPC4. The histological progressive genetic model suggests that the molecular detection of precursor lesions and early cancers is possible as mutant K-ras genes shed from PanINs have been identified in stool, duodenal fluid, and pancreatic juice samples [21]. Research is attempting to identify markers in pancreatic fluid that could reliably identify high-grade PanINs [34].

Adenosquamous carcinoma is a rare variant of ductal adenocarcinoma that shows both glandular and squamous differentiation [35]. This variant appears to be more common in patients who have undergone previous chemoradiation therapy. The biologic behavior of adenosquamous carcinoma appears to be similar to that of ductal adenocarcinoma, with similar rates of perineural invasion, lymph node metastases, and dissemination [36].

Acinar cell carcinomas account for only 1% of pancreatic exocrine tumors. Acinar tumors are typically smooth, fleshy, lobulated, hemorrhagic, or necrotic. Histologically, they form acini, and the cells display an eosinophilic granular cytoplasm [37]. These tumors are more common in males, with a male-to-female predominance of approximately 3:1. The age of diagnosis is usually in the fifth to seventh decades. These tumors tend to be larger than ductal adenocarcinomas, often being larger than 10 cm and have a slightly better prognosis than patients with ductal carcinoma [38]. Therefore, surgical resection is the treatment of choice.

Pancreatoblastoma primarily occurs in children younger than 15 years of age. Most pancreatoblastomas have an allelic loss of chromosome 11p and molecular alterations in the APC/β-catenin pathway [39]. These are genetically different from other pancreatic neoplasms including ductal adenocarcinoma and lack K-ras, p53 and DPC4 alterations. Histologically these tumors contain nests of squamoid cells in a sea of uniform, undifferentiated cells. They have a relatively better prognosis and are closely related to hepatoblastomas [40].

Cystic fibrous bands: CT shows a honeycomb pattern of microlacunae with thin septa separating different segments and they can have a sunburst pattern of central calcification. Most SMAs are generally considered benign and not premalignant, although malignant behavior has been reported rarely (i.e., metastases to the liver or peripancreatic lymph nodes). Symptomatic cysts or cysts that cannot be differentiated from other potentially (pre)malignant cysts should be considered for surgical excision. Recently, it has been suggested that cysts greater than 4 cm in size should also be resected since they demonstrate a significant increased growth rate compared to smaller cysts [41-43].

Mucinous cystic neoplasms (MCNs)

Although much less common than PanINs, MCNs can also be precursors of infiltrating ductal adenocarcinoma of the pancreas [33]. As with PanINs, MCNs progress through stages of increasing dysplasia, from mucinous cystadenoma to borderline mucinous cystic neoplasm to mucinous cystic neoplasm with in situ carcinoma, finally to reach the stage of invasive adenocarcinoma. Mucinous cystic neoplasms are defined as mucin-producing cyst-forming epithelial neoplasms of the pancreas with a distinctive ovarian-type stroma. MCNs are more common in women, with a female-to-male ratio of 9:1, and the mean age at diagnosis is between 40 and 50 years, with a range of 14-95 years [44]. Most (90%) MCNs arise in the body or tail of the pancreas. The cysts usually measure from 1-3 cm in size and do not appear to communicate with the pancreatic ducts. The extent of invasive and in situ carcinomas in MCNs can be very focal. Therefore, a benign diagnosis cannot be established on biopsy alone and the lesions should be completely resected. The prognosis for patients with resected benign or borderline tumors is excellent. Patients with mucinous cystadenocarcinoma tend to do better than patients with ductal adenocarcinoma, with a 5-year survival of approximately 50% [45].

Intraductal papillary mucinous neoplasms (IPMNs) are mucin-producing lesions that range from benign adenomas to invasive carcinoma arising within the pancreatic ducts. They arise from tall, columnar, mucin-containing epithelium with or without papillary projections [46]. These neoplasms extensively involve the main pancreatic ducts and/or major side branches. They arise most frequently in the head of pancreas and lack an ovarian-type stroma. IPMNs affect males slightly more than females in 3:2 ratio and have a mean age at diagnosis of 65 years, ranging 25-95 years. Non-invasive IPMNs are graded histologically according to the degree of architectural and cytologic atypia, into IPMN with mild dysplasia (IPMN adenoma), IPMN with moderate dysplasia, and IPMN with marked (severe) dysplasia (carcinoma *in situ*) [47]. Main duct IPMNs tend to have higher degrees of dysplasia and are more often associated with an invasive carcinoma compared to the branch duct type. This main duct variant typically causes massive ductal dilation and obstruction symptoms long before invasive malignancy has developed; thus, resection is usually curative. Common presenting signs and symptoms include abdominal pain, pancreatitis, nausea and vomiting, diabetes mellitus, weight loss, jaundice and back pain. Serum oncoproteins, such as carcinoembryonic antigen and CA 19-9 levels, are usually normal unless the IPMN is associated with an invasive cancer. Computerized tomography usually reveals a dilated main pancreatic duct or a collection of cysts that represent dilated branch ducts. The finding of mucin extruding from a patulous ampulla of Vater is a classic, almost diagnostic, feature at endoscopy. ERCP demonstrates a dilated pancreatic duct, and filling defects, caused by intraluminal mucous plugs or papillary projections of the neoplasm itself. Magnetic resonance cholangiopancreatography (MRCP) may demonstrate ductal dilatation and mural nodules [48]. The international guidelines for management of IPMNs suggest that patients should be optimally managed with surgical resection [49]. The guidelines suggest that the branch-type IPMNs less than 3 cm can be safely observed if they are asymptomatic and have no concerning radiographic or cytopathologic evidence of malignancy (mural nodules or abnormal cytology of cyst fluid). The guidelines further suggest a management strategy for branch-type IPMNs based on size. For lesions less than 1 cm in size, management entails serial cross-sectional imaging. For lesions 1 to 3 cm, management entails cross-sectional imaging, endoscopic ultrasound, and cytology. In patients with lesions 1 to 3 cm in size, surgical management is considered for symptoms or concerning radiographic (mural nodules, main-duct dilation) or cytopathologic evidence of malignancy. For lesions greater than 3 cm, surgical management is often recommended even in the absence of other concerning features of malignancy. It should be noted that these guidelines are derived from expert opinion based upon retrospective data. As such, they too are subject to bias and should be considered in the context of the patient as a whole. We recommend the management of these patients on a case-by-case basis and derive at treatment algorithms within a dedicated multidisciplinary group. The goal of surgical therapy for IPMNs should be a complete surgical resection yielding negative margins for all invasive and noninvasive disease [49]. Patients with completely resected noninvasive IPMNs should undergo careful follow-up and surveillance for the development of recurrent disease. The prognosis for the benign forms of the disease appears to be significantly better than for invasive IPMNs. Although invasive IPMNs are associated with disease progression and death, the prognosis remains markedly better than for typical invasive ductal carcinoma with survivals of 72%, 58%, and 43% at 1, 2, and 5 years, respectively. It is unclear whether this fact is due to earlier presentation or differences in tumor biology [50].

Diagnosis and Staging

Presentation

Pancreatic cancer develops insidiously and the majority of patients have advanced disease at the time of diagnosis. About 70% of tumors develop in the head of the gland, a location that often leads to stricture of the intrapancreatic portion of the common bile duct and the development of jaundice. The early symptoms of pancreatic cancer are non-specific (epigastic and diffuse abdominal pain, bloating, flatulence, general malaise, diarrhea, vomiting, constipation) and can be easily missed. Late symptoms include localized abdominal pain, radiation to the back in cases of retroperitoneal infiltration, weight loss and jaundice [51]. Acute and chronic pancreatitis, acute cholecystitis, upper gastrointestinal hemorrhage, neuropsychiatric disturbances, polyarthritis, painful skin nodules, pyrexia of unknown origin are also

possible presentations. Important signs include an upper abdominal mass, icterus, hepatomegaly, splenomegaly, palpable gallbladder (Courvoisier's sign), periumbilical nodules (Sister Mary Joseph's node), ascites, and peripheral edema. Migratory thrombophlebitis (Trousseau's sign) is reported in about 10% of pancreatic cancers and may be the only presenting sign. Physical signs usually indicate advanced disease. Tumors of the body and tail are often asymptomatic and usually present at an advanced stage owing to the vagary of their symptoms, and have a worse prognosis than those in the head of the gland [52]. Carcinomatosis may reveal itself by the presence of ascites, palpable tumor in the omentum, or pelvic tumor palpable on rectal examination (Blumer's shelf). Overall the most critical assessment to be made on clinical examination is an assessment of the patient's performance status, because this will dictate his or her suitability for surgical and nonsurgical therapy [53].

Imaging Evaluations

The goal of imaging in patients with suspected pancreatic cancer is to assess resectability since resection is the only potentially curative therapy. As such, the imaging modality selected should be able to comment on the relationship between the primary tumor and surrounding vasculature as well as sites of potential metastatic disease, namely the abdomen and (to a lesser extent) chest. In the authors' opinion, extensive imaging beyond cross-sectional imaging is not necessary and should be guided by the treating team. Similarly, invasive procedures, whether diagnostic or therapeutic, are preferably considered after consultation with an experienced pancreatic surgeon and/or a multidisciplinary team.

Pancreatic protocol CT is the most widely available and best validated imaging modality for diagnosing and staging patients with pancreatic cancer. Optimal multi-phase imaging technique (CT or MRI) [54] includes a non-contrast phase plus arterial and portal venous phases of contrast enhancement with thin cuts (3 mm or less) through the abdomen. This technique allows precise visualization of the relationship of the primary tumor to the mesenteric vasculature as well as detection of metastatic deposits as small as 3–5 mm. The difference in contrast enhancement between the parenchyma and adenocarcinoma is highest during the late arterial phase, thereby providing a clear distinction between a hypodense lesion in the pancreas and the rest of the organ [55].

Multi-phasic cross sectional imaging also allows for selective visualization of important arterial (eg: celiac axis, superior mesenteric artery [SMA], peripancreatic arteries) and venous structures (eg: superior mesenteric vein [SMV], splenic vein, portal vein [PV]), thereby providing an assessment of vascular invasion by the tumor. All of this information can improve the prediction of resectability. When evaluating a patient for operation, the following criteria are used to determine potential resectability: (1) no evidence of extrapancreatic or distant metastatic disease, (2) patency of the PV and SMV confluence, and (3) no involvement of the celiac axis or SMA [56].

Magnetic Resonance Imaging (MRI) is capable of providing staging information similar to that from a CT scan and can be performed in patients with allergies to CT contrast with the added advantage of cholangiopancreatography (MRCP) [57] to aid in delineating the anatomy of the biliary tree and the pancreatic duct in addition to contrast enhanced magnetic resonance angiography to show vascular invasion. At present, MRI for pancreatic cancer staging is generally limited to instances in which patients cannot receive CT contrast, because it offers no other major advantages over CT and is a more expensive imaging modality [57].

Endoscopic Ultrasonography: When tumors are small or poorly visualized on CT, endoscopic ultrasonography (EUS) provides a minimally invasive method of defining the extent of the primary tumor/vessel relationships and evaluating surrounding lymph nodes. [58] EUS is currently the method of choice for obtaining a pathologic diagnosis of malignancy. This technique produces high resolution images of the pancreas using a high frequency ultrasound probe at the end of an endoscope placed in the stomach and duodenum in close proximity to the pancreas. It has accuracy for detecting local invasion and nodal metastases from pancreatic cancer similar to that of dual phase multislice multidetector CT, which also provides information about hepatic metastases. The side-viewing duodenoscope [59] that delivers the ultrasound probe also permits the detection of ampullary and duodenal carcinomas and targeted fine needle aspiration or core biopses can be taken transduodenally under ultrasound guidance. EUS-guided fine needle aspiration is our preferred method for obtaining diagnostic biopsy. It should be noted, however, that definitive diagnosis is not always necessary before embarking upon curative-intent surgery.

Endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC)

The role of endoscopic retrograde cholangiopancreatography (ERCP) in the evaluation of pancreatic cancer is confined to palliation of obstructive jaundice, particularly in patients who are not candidates for surgery [60]. ERCP has no role in staging pancreatic cancer except as a means to rule out alternative causes of biliary obstruction such as choledocholithiasis and benign stricture in patients with atypical clinical presentation. A recent National Institutes of Health consensus conference concluded that ERCP and stent placement should not be routinely performed before pancreaticoduodenectomy in the presence of a clear low-density mass on CT scan [41].

Biliary decompression

ERCP and PTC allow the insertion of biliary stents and a combined PTC-ERCP approach may be necessary if access is difficult. Preoperative biliary stenting is controversial. A recent meta-analysis has suggested that it did not offer benefit and should not be routinely done [60]. Stenting provides ideal palliation for patients with jaundice who have unresectable or metastatic disease or are not fit for resection. Expandable metal stents offer excellent palliation [61]. On the basis of current evidence, ERCP/PTC and stenting should not be used routinely in patients with resectable tumors because it may increase the rate of septic postoperative complications [5]. Pragmatically, stenting may be necessary if it is anticipated that surgery will not be undertaken for several weeks or if the concentration of bilirubin in serum is rising rapidly. Again, it is preferred that the decision to undertake biliary decompression be made in the context of a multi-disciplinary team or after consultation with an experienced pancreatic surgeon.

Positron Emission Tomography (PET) is a non-invasive imaging tool that provides metabolic (rather than morphological) information on tumors. Malignant tissues show a higher uptake of fluorodeoxyglucose than normal surrounding tissues [62]. PET is sometimes useful in diagnosis of small tumors (<2 cm) and in the detection of extrapancreatic disease (eg: peritoneal or omental

metastases). Anatomical and functional imaging can be obtained simultaneously using PET-CT. However, current guidelines do not support routine PET in the work-up of pancreatic cancer [63].

Staging System for Pancreatic Cancer

Recently updated, the American Joint Committee on cancer (AJCC) TNM staging system is used for the uniform staging of pancreatic cancer [64]. In this system, disease stage is determined by three factors: (1) the size of the primary tumor and its relationship to the celiac axis and superior mesenteric artery (T); (2) the presence or absence of regional lymph node involvement (N), and (3) the presence or absence of distant metastases (M). Cancers diagnosed as stage I by preoperative imaging are small and localized to the pancreas, and are therefore routinely resectable. Stage II disease is characterized by a primary tumor that extends into adjacent organs or involves regional lymph nodes, without distant metastases or invasion into the celiac trunk or superior mesenteric artery. Such disease is also often resectable. Significantly, the most recent edition of the AJCC system includes tumors with isolated portal or superior mesenteric vein involvement in this group, reflecting the increasing perception of such tumors as potentially amenable to surgery. Patients with stage III disease have locally advanced disease which involves the major arteries, and those with stage IV cancer are found to have distant metastases at the time of diagnosis. Neither group is typically eligible for surgical resection. Instead, patients with stage III or IV disease are considered for clinical therapeutic trials and are typically offered palliative treatment designed to minimize symptoms of cholestasis and duodenal obstruction. This may take the form of surgical biliary-enteric bypass or endoscopic biliary stenting. While determination of resectability can generally be determined by high quality cross sectional imaging with interpretation by an experienced pancreatic surgeon, complete assessment may require laparotomy, at which time the relationship of the tumor to adjacent vessels can be assessed and histological analysis of tissue samples can be performed. The use of any preoperative staging modality is therefore limited, and must be used carefully in order to minimize the number of false-positives (patients with unresectable disease subjected to laparotomy) and false negatives (patients with resectable disease denied potentially curable surgical treatment based on an incorrect assumption of unresectability). The available diagnostic modalities differ in each of these regards, and therefore a combination of techniques must be employed in a logical and stepwise manner to most accurately determine disease stage prior to laparotomy [65].

Biomarkers

The clinical role of tumor markers has been limited and no tumor marker has been shown to be useful in the screening of an asymptomatic population. The standard serum marker, sialylated Lewis blood group antigen CA19-9 [66], is widely used, but its use is limited to monitoring responses to therapy, not as a diagnostic marker [67]. As a marker for early pancreatic cancer, there are some important weaknesses noted as follows: a) Approximately 10% of the population with the Lewis-negative genotype is not able to produce CA19-9 secondary to a lack of the enzyme involved in its synthesis, even if they have advanced pancreatic cancer; b) Patients with small pancreatic cancers often show false negative CA19-9 [68] values, thus eliminating its value in early diagnosis; c) CA19-9 elevation is common in patients with obstructive jaundice even without malignancy because of the reduction in clearance by the cholestatic liver; d) False positive CA19-9 elevation is also frequently observed in patients with cancers of the upper gastrointestinal tract, ovarian cancer, hepatocellular cancer, benign conditions of the hepatobiliary system and chronic pancreatitis. Thus CA19-9 is considered the standard for monitoring response to chemotherapy and recurrence following surgical resection in patients with pancreatic cancer, but not for the initial diagnosis of the disease. Due to the inability of CA19-9 to identify early potentially curable disease, several other serologic markers have been studied, including carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) [69], MIC1[70], carcinoembryonic antigen (CEA) [71], alpha-fetoprotein (AFP) [72], pancreatic associated antigen (SPan-1) [73], CA50 antigen, DU-PAN-2, alpha4GnT, cytokeratin-19 (CK-19) mRNA, elastase-1, tissue polypeptide antigen and tissue polypeptide-specific antigen. Unfortunately, none of these markers have achieved the levels of sensitivity and specificity necessary to be recommended as a screening tool for asymptomatic patients in the general population.

Recently, Gold et al. [74] developed the monoclonal antibody PAM4 which is highly specific for a glycoprotein produced by pancreatic cancer, MUC1. This antigen is identified in over 90% of pancreatic cancer and its precursor lesions, but is not detected in normal pancreas. They demonstrated that the sensitivity and specificity of the immunoassay for pancreatic cancer were 77% and 95%, respectively. In their study, both immunohistochemical and enzyme-linked immunoassays were used to detect and quantify PAM4-mucin in tissue and sera, respectively, of normal and cancer patients in whom staging of cancer is known. The data suggest that PAM4 [75] has potential utility as a biomarker in the early detection of pancreatic cancer. Genetic and epigenetic markers have been extensively investigated in pancreatic fluid. Protein markers require accurate quantification, and their levels may be quite variable in pancreatic fluid in normal individuals, whereas initial studies of genetic and epigenetic markers anticipate that the mere detection of such alterations would have some diagnostic value. Some of the genetic and epigenetic markers that have been investigated in pancreatic fluid include mutant K-ras, p53 mutations, DNA methylation alterations, and mitochondrial DNA mutations [28]. Over 300 microRNAs have been identified, and widespread alterations in these microRNAs have been identified in various types of cancer. While the expression of most microRNAs appears to be reduced in cancer, several are overexpressed and could be potential targets for early detection assays [76].

Principles of management

The only curative therapy for pancreatic cancer is surgical resection [32,77]. Determination of resectability relies on several patient- and tumor-related factors. Given the magnitude of the operations necessary to completely extirpate a malignant pancreatic tumor, patients must be of good enough health and performance status to withstand the physiologic challenges of pancreatectomy. These factors should be considered by an experienced pancreatic surgeon and not necessarily biased solely by patient age [78]. In addition, tumors must be confined to the region of dissection for a standard resection without involvement of critical contiguous structures. As such, tumors are classified as resectable [77], borderline resectable [79], or unresectable [80,81] (locally advanced or metastatic disease) tumors based upon the relationships between tumor and surrounding vasculature. Accepted definitions for resectability are:

Resectable tumors: Tumors considered localized and clearly resectable should demonstrate no distant metastasis, no radiographic evidence of superior mesenteric vein (SMV) or portal vein (PV) distortion and clear fat planes around the celiac axis, hepatic artery and superior mesentery artery (SMA).

Borderline resectable: Tumors considered borderline resectable include no distant metastasis, venous involvement of SMV or PV with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal allowing for safe resection and replacement. Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery without extension to the celiac axis and/or tumor abutment of the SMA not exceeding greater than 180 degrees of the circumference of the vessel wall are also included in borderline resectable tumors.

Unresectable (Locally advanced disease or distant metastases): Tumors considered to be unresectable demonstrate distant metastasis, greater than 180 degrees SMA encasement, any celiac or inferior vena cava abutment, unreconstructible SMV/portal occlusion, or aortic invasion or encasement.

Overall, the likelihood of attaining negative surgical margins (i.e. R0 resection) is the key criterion for consideration when determining whether a patient is a potential candidate for resection.

Surgery for Pancreatic Cancer: Criteria for resection

Surgical resection is the only potentially curative therapy for pancreatic cancer [81]. However more than 80% of patients present with advanced disease that cannot be cured with surgical resection. The median survival of completely resected patients ranges from 18 to 24 months and the actuarial 5 year survival rate is approximately 20% [82]. Ultimate disease control remains poor owing to the high incidence of both local and distant tumor recurrence. Once considered high-risk surgery, pancreatectomy now carries operative mortalities of less than 5% in experienced high volume centers [83]. In the most experienced hands, however, risk of recurrence is high with lymph node metastasis being the strongest predictor of long-term survival. Less predictive but certainly important factors include DNA content, tumor size, and margin status. Decisions about diagnostic management and resectability should always involve multidisciplinary [84] consultation with utilization of appropriate high quality imaging studies to evaluate the extent of disease.

Resection with curative intent: Although major advances have been made in the surgical management of pancreas cancer since the era of Whipple in the early 1900s, [85] the principal goal remains the same: removal of all gross and microscopic disease within the pancreas and draining lymph nodes, a so-called margin-negative or R0 resection. For lesions arising in the head of the gland, the three main surgical options for radical resection are the standard pancreaticoduodenectomy (attributed to Whipple), pylorus-preserving pancreaticoduodenectomy, and total pancreatectomy. The choice of operation does not appear to significantly impact survival and is more determined by surgeon choice and anatomic constraints. For lesions in the body and tail of the gland, distal pancreatectomy is the preferred approach.

The rationale for total pancreatectomy for carcinoma of the head of the pancreas is to eliminate multifocal disease, achieve wider lymphadenectomy, avoid spillage of tumor cells during transection of the pancreas, and avoid postoperative leakage from the pancreatic anastomosis [86]. These theoretic advantages have not translated into improved operative mortality or long-term survival. Total pancreatectomy has a higher operative mortality rate in most retrospective series compared to Whipple resection, and late deaths related to complications of brittle diabetes have traditionally been problematic [86]. However, with improvements in diabetes management and regulation of enzyme deficiency, total pancreatectomy remains a viable option when necessary for complete resection of a malignant or premalignant lesion. Notable is that total pancreatectomy does not add to survival or tumor control when partial pancreatectomy is possible. Similarly, extended lymphadenectomy does not improve survival over standard lymphadenectomy. However, extended lymphadenectomy is associated with increased early morbidity [87].

A surgical mortality of <5% has been achieved in most specialized centers but resection for pancreatic cancer continues to have a morbidity rate of >30% [83,88]. Complications following pancreatectomy include pancreatic fistulae, delayed gastric emptying, hemorrhage, wound infection, intraabdominal sepsis, acute pancreatitis, portal vein thrombosis, chylous ascites and bile leaks. In spite of this, reoperation rates are generally less than 10% and are often safely managed without long-term impact on overall survival or quality of life in experienced hands.

Adjuvant Therapy

Adjuvant chemotherapy in resected pancreatic cancer

In resected pancreatic cancer, studies investigating the role of adjuvant chemotherapy have demonstrated an improvement in clinical outcomes, showing a significant clinical benefit in comparison to observation. CONKO-001 investigated the use of adjuvant gemcitabine versus observation in resected pancreatic adenocarcinoma [89]. The primary endpoint, disease free survival, was reached with 13.4 months in patients who received adjuvant gemcitabine in comparison to 6.9 months in the observation group. The results were consistent across all subgroups including patients with R1 resections and node-positive disease. Updated results demonstrated a survival benefit, with a median overall survival of 22.8 months in the adjuvant gemcitabine group compared with 20.2 months (HR 0.76, p=0.01) in the observation [90]. A smaller phase III trial conducted in Japan showed similar findings to CONKO-001 [91]. ESPAC-3 compared adjuvant chemotherapy (5-Fluorouracil (5-FU) versus gemcitabine) versus observation in resected pancreatic cancer [92]. The observation group was discontinued early due to statistical evidence for a survival benefit from adjuvant chemotherapy. Similar therapeutic benefits were seen between adjuvant gemcitabine and bolus 5-FU, where a more favorable toxicity profile was associated with gemcitabine. Given these findings, there is a clear clinical benefit for adjuvant chemotherapy in patients with resected pancreatic adenocarcinoma, regardless of nodal and resection status.

The role of adjuvant chemoradiation therapy in resected pancreatic cancer

Randomized clinical trials investigating the role of combined chemoradiation therapy (CRT) have been underpowered, with flawed designs and mixed results. However, based on early phase III data, CRT remains a consideration in the adjuvant setting. The precedent for adjuvant CRT was based on the Gastrointestinal Tumor Study

Group (GITSG) 9173 trial that showed a clinical benefit from adjuvant 5-fluorouracil based chemoradiation therapy over observation, with a 9-month overall survival benefit (20 versus 11 months in the observation arm) [93]. The study was underpowered with only 43 subjects in the study accrued over a prolonged period of time. Subsequent studies attempting to confirm the benefit of adjuvant chemoradiation were unable to reproduce similar results. The EORTC trial, which compared adjuvant chemoradiation versus observation in resected pancreatic cancer, demonstrated a nominal and non-significant survival benefit [94]. The lack of clinical benefit may have been due to the inclusion of ampullary cancer, which has a considerably more favorable prognosis. Exploratory analysis demonstrated a survival benefit in patients with tumors located in the pancreatic head, with a 2-year survival of 34% versus 26% in the observation group (p=0.09). A more recent trial, RTOG 9704, investigated the use of concurrent chemoradiation with 5-Fluorouracil (5-FU) compared to gemcitabine. Despite using modern radiation therapies and quality control measures, no major differences in survival and local recurrence rates were seen between the two arms, with similar survival rates to that of CONKO-001, which utilized chemotherapy alone [95]. Noteworthy is that the design of RTOG 9704 was to compare two different chemotherapy agents in the adjuvant setting and thus does not settle the role of radiation therapy in the adjuvant setting.

Adjuvant chemotherapy versus chemoradiation therapy?

Currently, there is no clear indication when adjuvant concurrent chemoradiation should be used over chemotherapy. The only large randomized trial to investigate whether radiation benefits patients in the adjuvant setting was ESPAC-1 [93].

This complex trial examined the benefits of adjuvant chemoradiation and maintenance chemotherapy in pancreatic cancer. The trial was conducted in a 2 x 2 factorial design, which compared the use of chemoradiation, chemoradiation followed by chemotherapy, chemotherapy and observation.

While the study had several limitations including a high rate of protocol variations (i.e. absence of uniformity of treatments or absence of treatments in 30% of patients), allowing background therapy (chemoradiation or chemotherapy) and unconventional study design, it did show a survival benefit in the adjuvant chemotherapy arm while concurrent chemoradiation resulted in inferior clinical outcomes which included inferior survival, higher rates of recurrence and increased toxicities. Despite these results, the utility of adjuvant radiation therapy itself continues to be debated.

While acknowledging the limitations of cross-comparing studies, when looking at trials investigating adjuvant therapies in resected pancreatic cancer, the data shows a clear clinical benefit for adjuvant chemotherapy while the addition of radiation therapy seems unlikely to enhance the observed benefit with chemotherapy for all patients, likely owing to the high incidence of systemic failure.

Patients at a higher risk for local recurrence, including patients with microscopic or lymph node positive disease after resection, are thought to potentially derive benefit from radiation therapy [96]. By undergoing radiotherapy to the surgical margins, the process of "sterilizing" the site of micro-metastases is purported to delay or prevent locoregional recurrence.

However, when evaluating rates of locoregional recurrence, data from RTOG 9704 were similar to previous studies, including adjuvant chemotherapy trials (e.g. CONKO-001, JASPAC) [93] with rates of 36% and 31% for the 5-FU and gemcitabine arms, respectively. Additionally, it is uncertain whether improved local control translates to improved survival, which has yet to be seen in adjuvant chemoradiation trials.

An ongoing accruing prospective, randomized multi-institutional study (Clinical Trials.gov NCT01013649) is examining the role of radiation therapy after adjuvant chemotherapy and will hopefully provide clarity for its role in resected pancreatic cancer. Given these findings, the utility of radiation therapy in the post-operative setting is controversial at this time.

Treatment options for metastatic pancreatic cancer

Despite the prolonged standstill with limited therapeutic progress in pancreatic cancer, recent findings have led to a growing number of available therapeutic options for this disease. Prior to recent advances, the last significant therapy approved for pancreatic cancer was in 2007 based on a phase III randomized control trial where 569 patients were randomized to receive to either gemcitabine alone or the combination of gemcitabine plus erlotinib [97].

The study reached its primary endpoint that showed a survival improvement of arguably nominal clinical significance (6.2 vs. 5.9 months, HR 0.82, p=0.038) favoring the combination therapy.

Given the marginal gain in overall survival at the expense of significant toxicities (62% grade 3-4 toxicities) experienced with erlotinib, the combination therapy has never emerged as a viable therapeutic regimen in the treatment of pancreatic cancer. However, over the past several years, two combination chemotherapy regimens have emerged as new standards of care for the first-line treatment of metastatic pancreatic cancer, both based on randomized phase III trials. In the PRODIGE 4/ACCORD 11 trial, Conroy et al. demonstrated the superior efficacy of the FOLFIRINOX regimen (biweekly bolus plus infusional 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) when compared to single-agent gemcitabine in 342 patients with metastatic pancreas cancer [98].

Benefits in overall survival (11.1 vs. 6.8 months, HR 0.6, p<0.001) and progression free survival (6.4 vs. 3.3 months, HR 0.47, p<0.001) were observed in patients treated with the combination therapy versus gemcitabine alone. Shortly afterwards, Von Hoff et al. reported results from the MPACT trial, an international phase III study in which 861 patients were randomized to receive either gemcitabine alone or the combination of gemcitabine plus albumin-bound (nab-) paclitaxel (Abraxane, Celgene, Summit, NJ) [99].

The addition of this taxane agent resulted in an improved outcome, with a 1.8-month improvement in both overall survival (HR 0.72, p<0.001) and progression free survival (HR 0.69, p<0.001).

Despite these meaningful advances, the median survival in metastatic pancreatic cancer remains less than optimal with a desperate need to continue the developmental therapeutic path in pancreatic cancer. Table 1 summarizes key clinical trials in metastatic pancreatic cancer.

Chemotherapy Regimen	Survival, Median (months)	Hazard Ratio	Objective Response Rate	Toxicities (grade 3/4th)	Author References
Gemcitabine (versus 5-FU)	5.65 (vs. 4.41)	not reported	5.4	Neutropenia 25.9%	[93,100]
Gemcitabine + erlotinib (verus gemcitabine)	6.24 (vs. 5.9)	0.82	no significant difference (values not provided)	62% (Fatigue 15%, Infection 17%)	[97]
FOLFIRINOX (versus gemcitabine)	11.1 (vs. 6.8)	0.57	31.6	Fatigue 23.6% Neutropenia 45.7%	[98]
gemcitabine + nab-paclitaxel (versus gemctabine)	8.5 (vs 6.7)	0.72	23	Fatigue 17% Neutropenia 38%	[99]

Table 1: Summary of trials in metastatic pancreatic cancer.

Neoadjuvant Therapy (Preoperative)

The putative benefits of neoadjuvant therapyinclude increasing the likelihood that a higher proportion of resectable patients will receive chemotherapy and/or radiation; the potential to downsize tumors so as to increase the likelihood of a margin-free resection (ie, conversion to resectable status); the potential to select for surgery those patients with more stable disease or disease that is more responsive to therapy; and the treatment of micrometastases at an earlier stage [101,102]. Surgery is ideally performed 4 to 8 weeks after therapy. Surgery can be performed more than 8 weeks following therapy, but radiation-induced fibrosis may potentially make surgery more difficult. Delivery of neoadjuvant therapy necessitates durable biliary decompression for as many as 6 months in many patients with cancers of the pancreatic head.

Resectable disease: A number of studies have evaluated the use of neoadjuvant chemoradiation in patients with resectable disease [102]. The studies have suggested that preoperative therapy gives a selection advantage for surgical resection and for cost-effectiveness. Other potential advantages described are decreased incidence of pancreatic fistulas, increased rates of R0 resections and improved delivery of chemotherapy and radiosensitizing oxygenation. However no standardized clinical trial has been performed to recommend neoadjuvant therapy for most resectable patients. As such, neoadjuvant therapy should be offered to patients with resectable disease within the confines of a clinical trial.

Borderline Resectable Disease: With response rates exceeding 30% in FOLFIRINOX [103] and gemcitabine/nab-paclitaxel, the utilization of chemotherapy in the neoadjuvant setting has become an area of increased interest. Several small studies, including our institution, have examined the role of neoadjuvant chemotherapy, in combination with concurrent chemoradiation (if necessary). Our institutional experience has demonstrated that FOLFIRINOX in the neoadjuvant setting is tolerable and effective, with 51% of patients (including both borderline-resectable and locally advanced) with localized pancreatic cancer who received FOLFIRINOX were able to undergo successful resection of their disease [104]. Further studies investigating varying chemotherapy regimens in conjunction with radiation therapy are underway to assess and determine the optimal neoadjuvant regimen for localized pancreatic cancer (Clinical Trials.gov NCT00557492, NCT01359007).

Metastatic Disease: Palliation

Stents and surgery

Palliation of jaundice can be achieved by biliary stents (ERCP or PTC) or surgery. Patients with advanced tumors, should have biliary stent [105] insertion because they are unlikely to survive long, whereas patients with good performance status and small but unresectable tumors should have a surgical biliary bypass [106]. The median life of a plastic biliary stent is 6-10 weeks and expandable metal stents provide more prolonged palliation of obstructive jaundice [106].

Palliation of gastric outlet obstruction is achieved by a gastric bypass or by endoscopic placement of expandable metal stents in the duodenum [107]. An alternative for these patients with poor performance status is percutaneous endoscopic gastrostomy (PEG) tube placement. For a fit patient with a life expectancy greater than 3 to 6 months (ie, locally advanced disease) who develops gastric outlet obstruction, an open or laparoscopic gastrojejunostomy (duodenal bypass) with or without a jejunostomy (J) tube should be considered since it may provide more durable and effective palliation of gastric outlet obstruction than an enteral stent [108].

Pain management: Analgesics are recommended according to the WHO analgesics ladder [109]. Pain may be intolerable in advanced disease and endoscopic pancreatic duct decompression, ablation (percutaneous, endoscopic ultrasound-guided, laparoscopic or open) of the celiac ganglia using 5% phenol or 50% ethanol and the thoracoscopic division of the splanchnic nerves relieves pain [110]. Local radiation +/- chemotherapy may palliate pain.

Summary

The management of pancreatic cancer continues to be difficult with poor outcomes being common. While overall cure rates have not changed dramatically over the last several decades, we have seen improvements in palliative procedures, decreased morbidity and mortality of curative operations, and recent advances in systemic therapies. On the whole, this offers improved duration of life for incurable patients while maintaining quality of life. Still, nihilism for the disease prevails and often prevents potentially curable patients from seeking or being referred for aggressive therapy. Small but important recent steps in improved survival hope to focus light on the disease to provide the necessary interest and research afforded to many other cancers.

References

1. (2013) SEER cancer statistics review. National Cancer Institute.
2. Hartwig W, Hackert T, Hinz U, Gluth A, Bergmann F, et al. (2011) Pancreatic cancer surgery in the new millennium: better prediction of outcome. Ann Surg 254: 311-319.
3. Niederhuber JE, Brennan MF, Menck HR (1995) The National Cancer Data Base report on pancreatic cancer. Cancer 76: 1671-1677.
4. Ma J Siegel R, Jemal A (2013) Pancreatic cancer death rates by race among US men and women, 1970-2009. J Natl Cancer Inst 105: 1694-1700.
5. Gangl O, Fröschl U, Függer R (2014) Surgical quality data and survival after pancreatic cancer resections: a comparison of results for octogenarians and younger patients. Wien Klin Wochenschr 126: 757-761.
6. Yeo TP, Lowenfels AB (2012) Demographics and epidemiology of pancreatic cancer. Cancer J 18: 477-484.
7. Akushevich I, Kravchenko J, Ukraintseva S, Arbeev K, Kulminski A, et al. (2013) Morbidity risks among older adults with pre-existing age-related diseases. Exp Gerontol 48: 1395-1401.
8. Walker EJ, Ko AH, Holly EA, Bracci PM (2015) Metformin use among type 2 diabetics and risk of pancreatic cancer in a clinic-based case-control study. Int J Cancer 136: E646-653.
9. Wang Z, Lai ST, Xie L, Zhao JD, Ma NY, et al. (2014) Metformin is associated with reduced risk of pancreatic cancer in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Res Clin Pract 106: 19-26.
10. Sadeghi N, Abbruzzese JL, Yeung SC, Hassan M, Li D (2012) Metformin use is associated with better survival of diabetic patients with pancreatic cancer. Clin Cancer Res 18: 2905-2912.
11. Wang Y, Duan H, Yang X, Guo J (2014) Cigarette smoking and the risk of pancreatic cancer: a case-control study. Med Oncol 31: 184.
12. Fehringer G, Gallinger S, Borgida A, Zhang LR, Adams L, et al. (2014) The association of family history of cancer and medical history with pancreatic cancer risk. Pancreas 43: 812-814.
13. Borelli I, Casalis Cavalchini GC, Del Peschio S, Micheletti M, Venesio T, et al. (2014) A founder MLH1 mutation in Lynch syndrome families from Piedmont, Italy, is associated with an increased risk of pancreatic tumours and diverse immunohistochemical patterns. Fam Cancer 13: 401-413.
14. Lynch HT (2002) Phenotypic variation in eight extended CDKN2A germline mutation familial atypical multiple mole melanoma-pancreatic carcinoma-prone families: the familial atypical mole melanoma-pancreatic carcinoma syndrome. Cancer 94: 84-96.
15. Li D (2001) Molecular epidemiology of pancreatic cancer. Cancer J 7: 259-265.
16. Vyas O, Leung K, Ledbetter L, Kaley K, Rodriguez T, et al. (2015) Clinical outcomes in pancreatic adenocarcinoma associated with BRCA-2 mutation. Anticancer Drugs 26: 224-226.
17. Lal G, Liu L, Hogg D, Lassam NJ, Redston MS, et al. (2000) Patients with both pancreatic adenocarcinoma and melanoma may harbor germline CDKN2A mutations. Genes Chromosomes Cancer 27: 358-361.
18. Fleming JB, Minna JD (2002) Inactivation of tumor suppressor genes by promoter methylation is important in the pathogenesis of pancreatic cancer. Cancer Biol Ther 1: 297-299.
19. Neuman WL, Wasylyshyn ML, Jacoby R, Erroi F, Angriman I, et al. (1991) Evidence for a common molecular pathogenesis in colorectal, gastric, and pancreatic cancer. Genes Chromosomes Cancer 3: 468-473.
20. Matthaios D, Zarogoulidis P, Balgouranidou I, Chatzaki E, Kakolyris S (2011) Molecular pathogenesis of pancreatic cancer and clinical perspectives. Oncology 81: 259-272.
21. Laghi L, Orbetegli O, Bianchi P, Zerbi A, Di Carlo V, et al. (2002) Common occurrence of multiple K-RAS mutations in pancreatic cancers with associated precursor lesions and in biliary cancers. Oncogene 21: 4301-4306.
22. Hilgers W, Rosty C, Hahn SA (2002) Molecular pathogenesis of pancreatic cancer. Hematol Oncol Clin North Am 16: 17-35, v.
23. Oda Y, Aishima S, Morimatsu K, Shindo K, Fujino M, et al. (2014) Pancreatic intraepithelial neoplasia in the background of invasive ductal carcinoma of the pancreas as a prognostic factor. Histopathology 65: 389-397.
24. Maitra A, Kern SE, Hruban RH (2006) Molecular pathogenesis of pancreatic cancer. Best Pract Res Clin Gastroenterol 20: 211-226.
25. Pavelic J (2014) Editorial: combined cancer therapy. Curr Pharm Des 20: 6511-6512.
26. Hua YQ, Ouyang HQ, Chen Z, Meng ZQ, Luo JM, et al. (2011) Promoted cancer growth by stimulating cell proliferation and decreasing apoptosis using a lentivirus-based EphB2 RNAi in pancreatic carcinoma CFPAC-1 cells. Biomed Pharmacother 65: 123-131.
27. Rachagani S, Torres MP, Kumar S, Haridas D, Baine M, et al. (2012) Mucin (Muc) expression during pancreatic cancer progression in spontaneous mouse model: potential implications for diagnosis and therapy. J Hematol Oncol 5: 68.
28. Singh S, Chitkara D, Kumar V, Behrman SW, Mahato RI (2013) miRNA profiling in pancreatic cancer and restoration of chemosensitivity. Cancer Lett 334: 211-220.
29. Mathur A, Zeiger MA (2014) Genomic medicine for cancer prognosis. J Surg Oncol.
30. Mathew E, Zhang Y, Holtz AM Kane KT Song JY, et al. (2014) Dosage-dependent regulation of pancreatic cancer growth and angiogenesis by hedgehog signaling. Cell Rep 9: 484-494.
31. Esposito I, Konukiewitz B, Schlitter AM, Klöppel G (2014) Pathology of pancreatic ductal adenocarcinoma: facts, challenges and future developments. World J Gastroenterol 20: 13833-13841.
32. Rossi ML, Rehman AA, Gondi CS (2014) Therapeutic options for the management of pancreatic cancer. World J Gastroenterol 20: 11142-11159.
33. Distler M, Aust D, Weitz J, Pilarsky C, Grützmann R (2014) Precursor lesions for sporadic pancreatic cancer: PanIN, IPMN, and MCN. Biomed Res Int 2014: 474905.
34. Mirus JE (2014) Spatiotemporal proteomic analyses during pancreas cancer progression identifies STK4 as a novel candidate biomarker for early stage disease. Mol Cell Proteomics.
35. Imaoka H, Shimizu Y, Mizuno N, Hara K, Hijioka S, et al. (2014) Clinical characteristics of adenosquamous carcinoma of the pancreas: a matched case-control study. Pancreas 43: 287-290.
36. Komatsu H, Egawa S, Motoi F, Morikawa T, Sakata N, et al. (2015) Clinicopathological features and surgical outcomes of adenosquamous carcinoma of the pancreas: a retrospective analysis of patients with resectable stage tumors. Surg Today 45: 297-304.
37. Chaudhary P, Ranjan G, Chaudhary A, Tiwari AK, Arora MP (2013) Acinar cell carcinoma: a rare pancreatic malignancy. Clin Pract 3: e18.
38. Cananzi FC, Jayanth A, Lorenzi B, Belgaumkar A, Mochlinski K, et al. (2013) "Chronic" metastatic pancreatic acinar cell carcinoma. Pancreatology 13: 549-552.
39. Ismael O, Shimada A, Hama A, Takahashi Y, Sato Y, et al. (2012) Congenital pancreatoblastoma associated with Î²-catenin mutation. Pediatr Blood Cancer 58: 827.
40. Salman B, Brat G, Yoon YS, Hruban RH, Singhi AD, et al. (2013) The diagnosis and surgical treatment of pancreatoblastoma in adults: a case series and review of the literature. J Gastrointest Surg 17: 2153-2161.
41. Scoazec JY, Vullierme MP, Barthet M, Gonzalez JM, Sauvanet A (2013) Cystic and ductal tumors of the pancreas: diagnosis and management. J Visc Surg 150: 69-84.
42. Limaiem F, Khalfallah T, Farhat LB Bouraoui S, Lahmar A, et al. (2014) Pancreatic cystic neoplasms. N Am J Med Sci 6: 413-417.
43. Antonini F (2014) Management of serous cystic neoplasms of the pancreas. Expert Rev Gastroenterol Hepatol pg: 1-11.
44. Tang X, Zhang J, Chen Y, Lan Z, Wang C (2014) [Pancreatic cystic neoplasms: a report of 139 cases]. Zhonghua Yi Xue Za Zhi 94: 442-445.

45. Palmucci S, Cappello G, Trombatore C, Tilocca C, Todaro R, et al. (2014) Cystic pancreatic neoplasms: diagnosis and management emphasizing their imaging features. Eur Rev Med Pharmacol Sci 18: 1259-1268.
46. Lariño Noia J (2013) [Latest advances in pancreatic tumors]. Gastroenterol Hepatol 36 Suppl 2: 90-97.
47. Kawada N, Uehara H, Nagata S, Tsuchishima M, Tsutsumi M, et al. (2014) Predictors of malignancy in branch duct intraductal papillary mucinous neoplasm of the pancreas. JOP 15: 459-464.
48. Campbell NM, Katz SS, Escalon JG, Do RK (2015) Imaging patterns of intraductal papillary mucinous neoplasms of the pancreas: an illustrated discussion of the International Consensus Guidelines for the Management of IPMN. Abdom Imaging 40: 663-677.
49. Chin JY, Pitman MB, Hong TS (2014) Intraductal papillary mucinous neoplasm: clinical surveillance and management decisions. Semin Radiat Oncol 24: 77-84.
50. Käppeli RM, Müller SA, Hummel B, Kruse C, Müller P, et al. (2013) IPMN: surgical treatment. Langenbecks Arch Surg 398: 1029-1037.
51. Kalser MH, Barkin J, MacIntyre JM (1985) Pancreatic cancer. Assessment of prognosis by clinical presentation. Cancer 56: 397-402.
52. Worni M (2013) Modest improvement in overall survival for patients with metastatic pancreatic cancer: a trend analysis using the surveillance, epidemiology, and end results registry from 1988 to 2008. Pancreas 42: 1157-1163.
53. Lariño Noia J (2014) [Pancreatic tumors: recent developments]. Gastroenterol Hepatol 37 Suppl 3: 98-106.
54. Tamm EP, Balachandran A, Bhosale PR, Katz MH, Fleming JB, et al. (2012) Imaging of pancreatic adenocarcinoma: update on staging/resectability. Radiol Clin North Am 50: 407-428.
55. Balachandran A, Bhosale PR, Charnsangavej C, Tamm EP (2014) Imaging of pancreatic neoplasms. Surg Oncol Clin N Am 23: 751-788.
56. Bhosale PR, Menias CO, Balachandran A, Tamm EP, Charnsangavej C, et al. (2013) Vascular pancreatic lesions: spectrum of imaging findings of malignant masses and mimics with pathologic correlation. Abdom Imaging 38: 802-817.
57. Lee ES, Lee JM (2014) Imaging diagnosis of pancreatic cancer: a state-of-the-art review. World J Gastroenterol 20: 7864-7877.
58. Gonzalo-Marin J, Vila JJ, Perez-Miranda M (2014) Role of endoscopic ultrasound in the diagnosis of pancreatic cancer. World J Gastrointest Oncol 6: 360-368.
59. Sata N, Endo K, Shimura K, Koizumi M, Nagai H (2007) A new 3-D diagnosis strategy for duodenal malignant lesions using multidetector row CT, CT virtual duodenoscopy, duodenography, and 3-D multicholangiography. Abdom Imaging 32: 66-72.
60. Zippi M, Traversa G, Pica R, De Felici I, Cassieri C, et al. (2014) Efficacy and safety of endoscopic retrograde cholangiopancreatography (ERCP) performed in patients with Periampullary duodenal diverticula (PAD). Clin Ter 165: e291-294.
61. Boulay BR, Parepally M (2014) Managing malignant biliary obstruction in pancreas cancer: choosing the appropriate strategy. World J Gastroenterol 20: 9345-9353.
62. Yamamoto T, Sugiura T, Mizuno T, Okamura Y, Aramaki T, et al. (2015) Preoperative FDG-PET predicts early recurrence and a poor prognosis after resection of pancreatic adenocarcinoma. Ann Surg Oncol 22: 677-684.
63. Wakabayashi H, Nishiyama Y, Otani T, Sano T, Yachida S, et al. (2008) Role of 18F-fluorodeoxyglucose positron emission tomography imaging in surgery for pancreatic cancer. World J Gastroenterol 14: 64-69.
64. Bilimoria KY, Bentrem DJ, Ko CY, Ritchey J, Stewart AK, et al. (2007) Validation of the 6th edition AJCC Pancreatic Cancer Staging System: report from the National Cancer Database. Cancer 110: 738-744.
65. Schnelldorfer T, Gagnon AI Birkett RT, Reynolds G, Murphy KM, et al. (2014) Staging laparoscopy in pancreatic cancer: a potential role for advanced laparoscopic techniques. J Am Coll Surg 218: 1201-1206.
66. Brown EG, Canter RJ, Bold RJ (2015) Preoperative CA 19-9 kinetics as a prognostic variable in radiographically resectable pancreatic adenocarcinoma. J Surg Oncol 111: 293-298.
67. Marengo E, Robotti E (2014) Biomarkers for pancreatic cancer: Recent achievements in proteomics and genomics through classical and multivariate statistical methods. World J Gastroenterol 20: 13325-13342.
68. Alexakis N, Gomatos IP, Sbarounis S, Toutouzas K, Katsaragakis S, et al. (2015) High serum CA 19-9 but not tumor size should select patients for staging laparoscopy in radiological resectable pancreas head and peri-ampullary cancer. Eur J Surg Oncol 41: 265-269.
69. Serra S, Asa SL, Bamberger AM, Wagener C, Chetty R (2009) CEACAM1 expression in pancreatic endocrine tumors. Appl Immunohistochem Mol Morphol 17: 286-293.
70. Baine MJ, Menning M, Smith LM, Mallya K, Kaur S, et al. (2011) Differential gene expression analysis of peripheral blood mononuclear cells reveals novel test for early detection of pancreatic cancer. Cancer Biomark 11: 1-14.
71. Liu L, Xu H, Wang W, Wu C, Chen Y, et al. (2015) A preoperative serum signature of CEA+/CA125+/CA19-9 â‰¥ 1000 U/mL indicates poor outcome to pancreatectomy for pancreatic cancer. Int J Cancer 136: 2216-2227.
72. He M (2014) A genome wide association study of genetic loci that influence tumour biomarkers cancer antigen 19-9, carcinoembryonic antigen and alpha fetoprotein and their associations with cancer risk. Gut 63: 143-51.
73. Tsutsumi K, Kawamoto H, Hirao K, Sakakihara I, Yamamoto N, et al. (2012) Monitoring of CA19-9 and SPan-1 can facilitate the earlier confirmation of progressing pancreatic cancer during chemotherapy. Pancreatology 12: 409-416.
74. Tholey RM, Lal S, Jimbo M, Burkhart RA, Blanco FF, et al. (2015) MUC1 Promoter-Driven DTA as a Targeted Therapeutic Strategy against Pancreatic Cancer. Mol Cancer Res 13: 439-448.
75. Han S, Jin G, Wang L, Li M, He C, et al. (2014) The role of PAM4 in the management of pancreatic cancer: diagnosis, radioimmunodetection, and radioimmunotherapy. J Immunol Res 2014: 268479.
76. Jimenez RE, Warshaw AL, Z'graggen K, Hartwig W, Taylor DZ, et al. (1999) Sequential accumulation of K-ras mutations and p53 overexpression in the progression of pancreatic mucinous cystic neoplasms to malignancy. Ann Surg 230: 501-509.
77. Okano K, Suzuki Y (2014) Strategies for early detection of resectable pancreatic cancer. World J Gastroenterol 20: 11230-11240.
78. Hartwig W, Werner J, Jäger D, Debus J, Büchler MW (2013) Improvement of surgical results for pancreatic cancer. Lancet Oncol 14: e476-485.
79. Chao YJ, Sy ED, Hsu HP, Shan YS (2014) Predictors for resectability and survival in locally advanced pancreatic cancer after gemcitabine-based neoadjuvant therapy. BMC Surg 14: 72.
80. Turner K (2014) Complete radiological response of an initially locally advanced unresectable pancreatic cancer to chemoradiotherapy using FOLFIRINOX regimen: Report of a case. Clin Res Hepatol Gastroenterol,
81. Karachristos A, Esnaola NF (2014) Surgical management of pancreatic neoplasms: what's new? Curr Gastroenterol Rep 16: 397.
82. Strobel O, Hackert T, Hartwig W, Bergmann F, Hinz U, et al. (2009) Survival data justifies resection for pancreatic metastases. Ann Surg Oncol 16: 3340-3349.
83. Distler M, Grützmann R (2012) [New aspects of surgery for pancreatic cancer. Principles, results and evidence]. Pathologe 33 Suppl 2: 258-265.
84. Cavalcante L, Kelsen DP, Yu KH (2014) Combined modality therapy in pancreatic adenocarcinoma: review and updates on a controversial issue. Curr Pharm Des 20: 6697-6701.
85. Bednar F, Simeone DM (2014) Recent advances in pancreatic surgery. Curr Opin Gastroenterol 30: 518-523.
86. Hartwig W, Gluth A, Hinz U, Bergmann F, Spronk PE, et al. (2015) Total pancreatectomy for primary pancreatic neoplasms: renaissance of an unpopular operation. Ann Surg 261: 537-546.

87. Tol JA (2014) Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). Surgery 156: 591-600.
88. Long J, Luo GP, Xiao ZW, Liu ZQ, Guo M, et al. (2014) Cancer statistics: current diagnosis and treatment of pancreatic cancer in Shanghai, China. Cancer Lett 346: 273-277.
89. Oettle H (2007) Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA 297: 267-277.
90. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, et al. (2013) Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA 310: 1473-1481.
91. Aoyama T, Katayama Y, Murakawa M, Asari M, Kanazawa A, et al. (2014) Risk factors for 6-month continuation of S-1 adjuvant chemotherapy for resected pancreatic cancer. Cancer Chemother Pharmacol 74: 1235-1240.
92. Neoptolemos JP, Moore MJ, Cox TF, Valle JW, Palmer DH, et al. (2012) Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. JAMA 308: 147-156.
93. Oettle H, Neuhaus P (2007) Adjuvant therapy in pancreatic cancer: a critical appraisal. Drugs 67: 2293-2310.
94. Thomas A, Dajani K, Neoptolemos JP, Ghaneh P (2010) Adjuvant therapy in pancreatic cancer. Dig Dis 28: 684-692.
95. Berger AC, Winter K, Hoffman JP, Regine WF, Abrams RA, et al. (2012) Five year results of US intergroup/RTOG 9704 with postoperative CA 19-990 U/mL and comparison to the CONKO-001 trial. Int J Radiat Oncol Biol Phys 84: e291-297.
96. Wang P, Meng ZQ, Chen Z, Lin JH, Zhou ZH, et al. (2008) Survival rate of pancreatic cancer in elderly patients. Hepatogastroenterology 55: 681-686.
97. (1988) Pancreatic cancer pain: presentation, pathogenesis and management. J Pain Symptom Manage 3: 163-209.
98. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, et al. (2011) FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364: 1817-1825.
99. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, et al. (2013) Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 369: 1691-1703.
100. Li CP (2003) Concurrent chemoradiotherapy treatment of locally advanced pancreatic cancer: gemcitabine versus 5-fluorouracil, a randomized controlled study. Int J Radiat Oncol Biol Phys 57: 98-104.
101. Habermehl D, Kessel K, Welzel T, Hof H, Abdollahi A, et al. (2012) Neoadjuvant chemoradiation with Gemcitabine for locally advanced pancreatic cancer. Radiat Oncol 7: 28.
102. Quiros RM, Brown KM, Hoffman JP (2007) Neoadjuvant therapy in pancreatic cancer. Cancer Invest 25: 267-273.
103. Conroy T, Gavoille C, Samalin E, Ychou M, Ducreux M (2013) The role of the FOLFIRINOX regimen for advanced pancreatic cancer. Curr Oncol Rep 15: 182-189.
104. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, et al. (2010) Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA 304: 1073-1081.
105. Krokidis M (2011) Percutaneous palliation of pancreatic head cancer: randomized comparison of ePTFE/FEP-covered versus uncovered nitinol biliary stents. Cardiovasc Intervent Radiol 34: 352-361.
106. Ueda J, Kayashima T, Mori Y, Ohtsuka T, Takahata S, et al. (2014) Hepaticocholecystojejunostomy as effective palliative biliary bypass for unresectable pancreatic cancer. Hepatogastroenterology 61: 197-202.
107. Jeurnink SM, Steyerberg EW, van Hooft JE, van Eijck CH, Schwartz MP, et al. (2010) Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial. Gastrointest Endosc 71: 490-499.
108. Jeurnink SM, van Eijck CH, Steyerberg EW, Kuipers EJ, Siersema PD (2007) Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. BMC Gastroenterol 7: 18.
109. Wong GY, Schroeder DR, Carns PE, Wilson JL, Martin DP, et al. (2004) Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: a randomized controlled trial. JAMA 291: 1092-1099.
110. Wong GY, Sakorafas GH, Tsiotos GG, Sarr MG (1999) Palliation of pain in chronic pancreatitis. Use of neural blocks and neurotomy. Surg Clin North Am 79: 873-893.