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Diagnosis and Management of Pancreatic Cancer

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Abstract

Background—Pancreatic adenocarcinoma is an aggressive malignancy with the majority of patients dying within one year of diagnosis. While surgical resection with negative margins offers the only hope for cure only a small minority of patients are amenable to resection at the time of diagnosis owing to the propensity for early metastasis. While most advances in the last several decades have revolved around improvements in surgical techniques and postoperative outcomes, some modest inroads have been made with modern chemotherapy. This review discusses the diagnosis and management of pancreatic cancer and highlights some of the current issues.

Methods—A Medline database search was performed to identify relevant articles using the keywords “pancreatic adenocarcinoma” “diagnosis” “CA19-9” “pancreaticoduodenectomy” “adjuvant therapy” “chemotherapy”, and “microRNA”. Additional papers were then identified by a manual search of the references from the key articles.

Results—While high quality CT is often the only imaging modality needed for preoperative evaluation, magnetic resonance imaging (MRI), cholangiography, and endoscopic ultrasound (EUS) have been utilized for diagnosis, staging, and/ or palliation. The controversies of pylorus preservation, extended lymphadenectomy, and laparoscopic pancreaticoduodenectomy are discussed. Randomized controlled trials regarding the use of 5-fluorouracil and gemcitabine are also reviewed.

Conclusion—Early detection and aggressive surgical resection in combination with protocol-driven adjuvant therapy and novel molecular approaches are the only hope for cure. This review summarizes the recent literature on the abovementioned topics.

Keywords

pancreatic adenocarcinoma; diagnosis; CA19-9; pancreaticoduodenectomy; adjuvant therapy; chemotherapy; microRNA

Introduction

In 2008, the American Cancer Society estimated that 37,680 Americans would be diagnosed with pancreatic cancer and that approximately 34,290 would die from the disease. [1] The majority of patients with pancreatic cancer die within one year of diagnosis, and only about four percent go on to be long-term survivors. [2] As a result, pancreatic cancer is the fourth

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leading cause of cancer death overall in the United States with the peak age affected grouping their seventh decade of life. [3] Surgical resection with negative margins offers the only hope for cure; yet, only small minorities of patients are amenable to resection at the time of diagnosis owing to the propensity for early metastasis. [3] Even in the best of circumstances, when patients are able to undergo margin-negative resection with pathologically negative regional lymph nodes, 5-year survival rates only range 7–25%, with median survivals of 11–20 months. [3] The poor survival rates are partially due to stage migration, but equally important is the biology of pancreatic adenocarcinoma with aggressive local invasion, early metastasis, and resistance to chemotherapy and radiation. While survival in many cancers has improved over the last few decades, pancreatic cancer has seen modest progress. [1] Early detection and aggressive surgical resection in combination with protocol-driven adjuvant therapy and novel molecular approaches are the only hope for cure. Herein, we will discuss current recommendations for the diagnostic work-up and management of pancreatic cancer. While discussion of risk factors and precursor lesions such as pancreatic intraductal neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm (MCN) are no less important, they deserve a more thorough focus, which is beyond the scope of this review.

Diagnosis and Work-up

Aside from serendipitous identification of a pancreatic mass during axial imaging for an unrelated problem, early diagnosis of pancreatic mass relies upon a high index of suspicion since many of the symptoms of abdominal discomfort, back pain, early satiety, fatigue, and weight loss are non-specific and usually not related to malignancy. However, the classic sign of painless jaundice is the hallmark of pancreatic cancer. Often accompanied by steatorrhea, biliary obstruction may also result in subclinical elevation of transaminases and alkaline phosphatase, dark urine, and/ or pruritus. [2] New onset type 2 diabetes may precede other signs or symptoms of pancreatic cancer and should be considered in patients over the age of 50, particularly when associated with abdominal pain or unintentional weight loss. [4, 5]. Unexplained pancreatitis or, less commonly, a palpable upper abdominal mass similarly may be a harbinger of a pancreatic mass, albeit often a late sign.

Diagnostic work-up when there is clinical suspicion of pancreatic cancer often begins with a Spiral Computed Tomography (CT) scan to identify intra- and extrahepatic biliary dilation, pancreatic ductal dilation and pancreatic mass. CT scans for diagnosis and staging should be performed according to a defined pancreas protocol such as triphasic cross-sectional imaging with thin slices (0.625 to 1.5mm) through the pancreas. [6, 7] While considering the diagnosis of pancreatic cancer, axial imaging should be of sufficient quality so as to determine resectability as well. Such imaging can be used to classify the pancreatic mass as resectable, borderline resectable, or unresectable. A clearly resectable lesion refers to the absence of involvement of the celiac axis of the superior mesenteric artery (SMA), along with demonstration of patency of the portal and superior mesenteric veins (SMV) without evidence of metastatic disease. [8] Conversely, distant metastatic disease, direct extension to celiac artery or greater than 180 degree encasement of the superior mesenteric artery, unreconstructable portal vein or superior mesenteric vein occlusion, or aortic encasement/ invasion, qualify tumors as unresectable. [9] Borderline resectable lesions includes tumors

that have portal or superior mesenteric vein impingement, tumor abutting the SMA with less than 180 degree encasement, gastroduodenal artery encasement at its origin, encasement of the hepatic artery if amenable to resection and reconstruction, limited inferior vena cava invasion, and/ or short segment SMV occlusion, if reconstructable. [9]

While high quality CT is often the only imaging modality needed for preoperative evaluation, magnetic resonance imaging (MRI), cholangiography, and endoscopic ultrasound (EUS) have been utilized for diagnosis, staging, and/ or palliation. [2] MRI offers high resolution imaging with the added benefit of cholangiography and pancreatography (MRCP). Beyond the avoidance of ionizing radiation, MRI/MRCP offers little clinical advantage in staging or preoperative planning over spiral CT but with significant increase in cost. [10] As such, CT remains the initial imaging modality of choice unless contraindications exist such as a contrast allergy.

Endoscopic ultrasound (EUS) has been adopted into numerous interventional techniques that may help improve the diagnosis and management of pancreatic cancer. EUS-guided fine needle aspiration is now being recommended as a procedure of choice over CT guided biopsy for tissue diagnosis of pancreatic cancer for its theoretical lower risk of peritoneal seeding from biopsy. [8] It should be mentioned here, however, that tissue confirmation is not mandated prior to surgical exploration for presumed pancreatic cancer nor should a nondiagnostic biopsy result delay definitive care as set forth in the practice guidelines of the National Comprehensive Cancer Network. [11] The role of EUS in the management of pancreatic cancer is still being defined. The proximity of the pancreas to the posterior wall of the stomach and the duodenal bulb coupled with modern high frequency ultrasound probes allows assessment of the relationship between the pancreatic mass and aforementioned vascular structures to determine resectability. [12, 13] Still, EUS does not offer significant improvement in assessment of resectability over high quality CT unless no mass is obvious. [13, 14] Probably the most exciting potential benefit of EUS in pancreatic cancer is the ability to deliver novel treatments through direct fine needle injection.

In the absence of a mass on high quality axial imaging in patients suspected to have pancreatic cancer, additional imaging of the ductal anatomy by cholangiography may be indicated. Cholangiography can be undertaken via percutaneous transhepatic (PTC) approach or via an endoscopic retrograde approach in conjunction with pancreatography (ERCP). ERCP is particularly useful in patients with equivocal CT findings since pancreatic cancer is rarely associated with normal pancreatography. [10] The impact of preoperative biliary stenting has been the subject of debate for many years. Given the perceived increased morbidity and mortality associated with pancreatectomy in the face of severe hyperbilirubinemia, routine biliary decompression was commonly undertaken at many centers. [15, 16] This practice was called into question as data began to emerge from high volume centers reporting increased rates of pancreatic fistula and wound complications in patients with preoperative biliary stents. [17, 18] However, as level 1 evidence emerged, preoperative biliary stenting was found to not have any impact (positive or negative) on perioperative morbidity or mortality nor did it impact oncologic outcomes. [19, 20, 21] As such, biliary decompression, via ERCP or PTC, is reserved for those patients in whom surgical resection is not planned or needs to be delayed.

Tumor markers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) have been proposed for use in both diagnosis and surveillance of pancreatic cancer but have not been proven to be highly sensitive or specific to pancreatic cancer. [2] We have shown that in 118 patients who had undergone pancreatic resection for benign or malignant lesions, the sensitivity and specificity of elevated CA19-9 alone was 76% and 92% respectively. [22] However, when considered in the context of age over 50 years and jaundice, specificity for pancreatic cancer was improved to 92%.At higher levels, especially greater than 150 U/mL, sensitivity for malignancy was 93%- 95% of patients presenting with jaundice.CA19-9 levels have also been considered as determinates of resectability by receiver operating characteristic (ROC) curve analysis. Preoperative levels greater than 353 U/mL predicted unresectability with a sensitivity and specificity of 93% and 78% respectively. [23] False positive tests with CA19-9 can result from biliary obstruction, while false negative tests can occur in up to 5% – 10% of the population who are negative for the blood type antigen Lewis A. [22]

Surgical Management

Radical pancreatectomy with regional lymphadenectomy is the mainstay of curative therapy for pancreatic cancer with the ultimate goal of complete removal of all macroscopic and microscopic disease (i.e. R0 resection). Still, even in optimal situations where complete resection of node-negative disease is possible, median survivals are approximately 18–24 months with 5-year survival of 20% or less. [24] The strongest predictor of survival following resection remains lymph node status. [25] The type and extent of resection is dictated by tumor location and involvement of surrounding structures; distal or subtotal pancreatectomy for tumors of the left pancreas and pancreaticoduodenectomy for tumors to the right of the vessels. The less common central pancreatectomy may be considered for tumors of neck or mid-body of the pancreas.[26]

Pancreaticoduodenectomy, (PD), also known as the Whipple procedure, has been regarded as the standard operation for pancreatic head and uncinate lesions. Once associated with prohibitive morbidity and mortality rates, the operation can be safely undertaken with an expected mortality of 2% or less and a morbidity of 30% – 40% in high-volume centers. [26, 27] Given the safety with which the operation can now be undertaken, few technical issues remain topics of discussion; in particular, the management of the pylorus, the extent of lymphadenectomy, the role of vein resection, and the definition of the retroperitoneal margin are of continued interest. Pylorus preservation, first described in 1978 by Traverso and Longmire, [28] was hypothesized to provide a more physiologic reconstruction to allow improved nutrition. Subsequent prospective randomized studies, while showing reduction in operative times relative to standard PD, have failed to demonstrate improvements in quality of life or nutritional status following resection. [29, 30, 31, 32, 33] As well, the most common “complication,” delayed gastric emptying does not seem to be influenced by the type of resection. As such, either approach is considered acceptable and is dictated by tumor extent and/or surgeon preference.

Given the dismal outcomes after resection with overall median survival of only 13 months and 5-year survival of 6.8% as accentuated by an analysis of 4005 patients who underwent

resection for pancreatic adenocarcinoma, some surgeons have advocated more radical approaches to include total pancreatectomy, extended lymph node dissection, and portal/mesenteric vascular resections. [34] The standard extent of lymphadenectomy was defined by an international congress in 1998 to include the region around the duodenum and pancreas, including the lymph nodes on the right side of the hepatoduodenal ligament, the right side of the superior mesenteric artery, and the anterior and posterior pancreaticoduodenal lymph nodes. [35] Resections that include lymph nodes outreaching these areas could therefore be considered an extended lymphadenectomy. However, Glanemann et al. found extended lymphadenectomy resulted in higher morbidity without improvement in survival, thus concluding that lymphadenectomy be confined to the aforementioned nodal basins. [36]

Unresolved is the role of venous resection to obtain negative margins for locally advanced lesions. Reports from high-volume centers demonstrate the safety of major venous resection without significant increases in mortality or morbidity rates following PD. [36, 37, 38] Intraoperative assessment of major venous involvement is often unreliable, yet overall survival does not seem to be decreased compared to lesions not involving superior mesenteric or portal veins provided complete tumor extirpation is possible. [37] As such, major venous invasion with or without short segment occlusion amenable to resection and reconstruction is not considered a contraindication to resection. However, neoadjuvant chemoradiation on or off protocol is recommended for these borderline resectable tumors. [39, 40, 41, 42] Experiences with resections of the visceral arteries, such as the superior mesenteric, celiac, or hepatic artery, are limited to case studies and small series. [26]. Given the paucity of data documenting an advantage to arterial resection for locally advanced pancreatic cancer, anticipated visceral arterial encasement >180 degrees is considered a contraindication to resection. [26]

The importance of defining pancreatic margins with an emphasis on complete (i.e. R0) resection has been emphasized in several recent reports [43, 44, 45, 46] There is little debate on what constitutes a negative pancreatic neck, duodenal, or bile duct margin. Less clear is the definition of the retroperitoneal and uncinate margins and the importance of margins less than one millimeter. [47, 48] While a survival advantage to a margin negative resection is not always demonstrable, intraoperative assessment of margin status increases the likelihood of R0 resection. [25]

As with most surgical techniques, there has been a push towards more minimally invasive techniques and the field of pancreatic cancer has not gone untouched. In 1993, the first laparoscopic Whipple procedure was described by Gagner et al. [49] Today, many still have not accepted the advancement and criticize it for technical difficulties, such as long operating times, longer hospitalizations secondary to delayed gastric emptying, and no improved survival. [50] A retrospective study by Palanivelu et al. of 42 patients who had undergone laparoscopic pancreatoduodenectomy found 5-year survival rates for all patients with malignancy, ampullary adenocarcinoma, pancreatic cystadenocarcinoma, pancreatic head adenocarcinoma, and common bile duct adenocarcinoma were 32%, 30.7%, 33.3%, 19.1%, and 50% respectively. [50] From the studies that have been performed thus far though, laparoscopic pancreatoduodenectomy has been proven a feasible option with at least

no poorer results than with open pancreatoduodenectomy. [36] The role of laparoscopy in the management of pancreatic adenocarcinoma remains open for debate as studies on laparoscopic Whipple procedures or laparoscopic distal pancreatectomies have unfortunately, had small sample sizes and have been performed without corresponding control groups, so further conclusions will not be able to be drawn until larger prospective studies are completed.

Palliative therapy

As nearly 75% of patients are not amenable to curative resection at the time of diagnosis, palliation of common problems such as pain, gastrointestinal obstruction, biliary obstruction, pancreatic insufficiency, anorexia/cachexia, and depression become paramount. [51] Up to 80% of patients complain of abdominal or back pain, typically from involvement of the splanchnic plexus or retroperitoneum. [51] Interventional pain management techniques can play a valuable role in pain control in pancreatic cancer. Neurolytic celiac plexus block can be performed under radiographic guidance using a posterior approach, laparoscopically, or by endoscopic ultrasound. [52, 53] A common side effect is diarrhea seen in about a third of the patients, which may result from sympathetic blockage of the GI tract. [51] Duodenal obstruction from local tumor growth may result in gastric outlet obstruction, necessitating gastrojejunostomy as a palliative measure. This has long term efficacy but has the drawback of a potentially prolonged postoperative course. Prophylactic gastrojejunostomy might be considered in patients found to be unresectable at the time of exploration but with limited tumor burden.[53] Expandable metal stents placed endoscopically for duodenal obstruction may be helpful in select patients but significant complications can occur including perforation, bleeding, stent malposition or migration, and occlusion by tumor overgrowth. [54] Although relief of mechanical obstruction is often possible, some patients do not experience symptom improvement after stent placement due to functional obstruction secondary to gastrointestinal dysmotility. [51]

Adjuvant therapy

In the best of circumstances, even with complete resection of all gross and microscopic disease, the vast majority of patients are doomed to failure due to distant metastatic disease and/or local recurrence, underscoring the need for adjuvant systemic therapy. The earliest adjuvant treatment offered to pancreatic cancer patients was a combined modality therapy of radiation and 5-Fluorouracil (5-FU), a thymidylate synthase inhibitor that interferes with DNA replication. [3] The Gastrointestinal Tumor Study Group (GITSG) in the 1970s and 1980s was the first randomized controlled trial to demonstrate that adjuvant chemo-radiotherapy using bolus 5-FU therapy conferred a survival benefit in patients with resected pancreatic cancer. [3] Patients that received the 5-FU regimen for two years had a two year survival of 43% compared with 18% in the control group which did not receive postoperative chemoradiation. [3] In spite of the remarkably slow accrual and inherent selection bias of the GITSG trial, 5-FU with radiation was the standard of care in the United States for more than twenty years. [55] The approval of gemcitabine in 1996 by the US Food and Drug Administration was the next major advancement in the treatment of pancreatic cancer since the approval of 5-fluorouracil almost thirty five years ago. [55] As a prodrug,

gemcitabine must be phosphorylated to its active metabolites gemcitabine diphosphate and gemcitabine triphosphate which inhibit DNA synthesis. [3] Interestingly, gemcitabine was approved not for its survival advantage, which was less than three weeks, but for its improvement in quality of life in patients with inoperable pancreatic cancer. [56] It wasn't until recently that the role of gemcitabine as adjuvant therapy would be elucidated. CONKO-001 was a multi-center, phase III randomized controlled trial conducted from 1998 to 2004 in Germany and Austria that enrolled 368 treatment-naïve pancreatic cancer patients following complete (i.e. R0/R1) resection. [57] Patients were randomized to receive adjuvant gemcitabine (n=179) or observation (n=175). Greater than 80% received R0 resections. Median follow-up was 53 months, during which 74% of patients in the gemcitabine group and 92% of patients in the control group developed recurrent disease. Median disease-free survival was significantly longer at 13.4 months in the gemcitabine group versus 6.9 months in the control group, although overall survival was not significantly different. [57]

The European Study Group for Pancreatic Cancer-1 (ESPAC-1) study, a landmark phase III randomized controlled trial, involved sixty-one cancer centers across eleven countries to enroll 541 patients following complete resection to assess the roles of chemotherapy and chemoradiation in the adjuvant treatment of pancreatic cancer. Patients were randomized prospectively into one of four arms of the study by resection margin status. [58] Similar median survival was seen between the 175 patients who received chemoradiation (15.5 months) and the 178 who were randomized to receive no chemoradiation(16.1 months). They did observe a significant difference in survival in patients who received chemotherapy with 5- fluorouracil compared to those allocated to no chemotherapy with median survivals of 19.7 months and 14.0 months, respectively. [58] The final conclusion was adjuvant chemoradiation has no survival benefit. However, the ESPAC-1 trial has been criticized for flaws in conduct and reporting and lack of quality control regarding its radiotherapy. [59, 60] In their critique of the ESPAC-1 trial, Evans et al. were concerned about the lack of standardization regarding pathologic assessment of surgical specimens, and problems with the 2 × 2 factorial design which led to limited ability to interpret analysis on some subsets of patients as information on the treatment received by those patients was not provided and the nonrandomized treatments were not standardized. [61] Noteworthy was that approximately 25% of patients had follow-up of less than one month at the time of analysis. Given the criticisms of this trial, 5- fluorouracil based chemoradiation is still considered an acceptable choice in the adjuvant setting, although many favor adjuvant chemotherapy alone. [62]

The RTOG-9704 trial, an intergroup trial conducted by the US National Cancer Institute and the Radiation Therapy Oncology Group, was designed to assess if the addition of gemcitabine to adjuvant 5-fluorouracil chemoradiation would improve survival for patients with resected pancreatic adenocarcinoma.[62] This large, multi-center, phase III randomized controlled trial conducted from 1998 to 2002 in 164 US and Canadian institutions enrolled 451 treatment-naïve patients following complete resection of pancreatic cancer. Patients were randomized to receive continuous infusion 5-FU (n=230) or weekly gemcitabine for three weeks prior to chemoradiation and for twelve weeks after chemoradiation therapy (n=221). Chemoradiation was the same for both groups with 50.4 Gy and continuous infusion of 5FU (250mg/m^2 per day). Patients with pancreatic head cancers treated with

gemcitabine and chemoradiation had a median survival of 20.5 months and a 3-year survival rate of 31% compared with those treated with 5-FU and chemoradiation who had a median survival of 16.9 months and a 3-year survival rate of 22% (P=0.09). Treatment tolerance was similar between groups with greater than 85% of patients completing chemotherapy and radiation therapy. The study concluded that the addition of gemcitabine to adjuvant 5FU based chemoradiation is associated with a survival benefit in patients with resected pancreatic head cancers, although the improvement was not statistically significant. [62] Given conflicting results of randomized controlled trials, there is ongoing debate over the optimal adjuvant therapy for pancreatic adenocarcinoma, thus emphasizing the need for ongoing enrollment in clinical trials. [3]

Molecular Biology

Research over the last decade has made great strides in uncovering the underlying genetic and molecular abnormalities that drive the development of pancreatic cancer. [63] Alterations to specific oncogenes, such as K-ras, and the loss of tumor suppressor genes, such as TP53, and p16INK4, are believed to play a crucial role in the development of pancreatic cancer. [64, 65] Several cellular proteins important for the control of cell cycle, proliferation, apoptosis, and invasiveness, such as Bcl-2, Akt, mdm2, and the human epidermal growth factor receptor (HER-1/EGFR) have been found to have altered expression in pancreatic cancer. [64, 65] The prevalence of these genetic alterations increases in direct correlation with the increasing severity of dysplasia seen in human pancreatic ductal mucosal lesions. [64] The inactivation of TP53 may help explain the relative resistance of some pancreatic tumors to 5-fluorouracil, whereas BCL-2 overexpression is associated with reduced sensitivity to gemcitabine. [65] Having a better understanding of the molecular and genetic abnormalities in pancreatic cancer has opened new areas of research for the development of molecular- targeted therapies and allowed therapy to become more individualized. [63]

An exciting new area of research in pancreatic cancer involves microRNA. MicroRNAs are small, 18–22 nucleotides, noncoding RNAs involved in the posttranscriptional modification of many target genes that are involved in cell proliferation, apoptosis, and differentiation. [66] While over 450 human microRNAs have been identified, microRNA-21 (miR-21) in particular has been implicated in multiple hematologic and solid organ malignancies, including pancreatic cancer. A study by Dillhoff et al. used in situ hybridization to evaluate the miR-21 expression in eighty resected pancreatic cancer, chronic pancreatitis, and benign pancreas specimens. They found miR-21 useful as a biomarker to distinguish between benign and cancerous tissues as none of the benign tissues demonstrated strong miR-21 expression, whereas the cancerous tissue had significant overexpression of miR-21. Dillhoff et al. also concluded that the strong miR-21 expression in patients with node-negative disease correlated with a decreased median survival from 27.7 months to 15.2 months, suggesting the potential future use of miR-21 as an important biological marker for outcome. [66] A similar study by Bloomston et al. which attempted to identify a microRNA expression profile that could distinguish between high- risk patients who could be considered long- term (i.e., > 24 months) and short- term survivors successfully identified a group of six microRNAs: miR-452, miR-105, miR-127, miR-518a-2, miR-187, and

miR-30a-3p. They also identified twenty-one microRNAs with increased expression and four with decreased expression that correctly differentiated pancreatic cancer from benign tissue in 90% of samples by cross validation. [67] The field of research involving microRNAs is quickly evolving and holds much potential for the diagnosis, prognosis, and treatment of pancreatic adenocarcinoma.

Conclusions

Despite ever increasing knowledge and experience with thousands of pancreatic cancer patients worldwide, very little improvement has been made in overall survival over the last three decades. Several important strides, however, have been made offering hope for the future. These include, but are not limited to, identification of precursor lesions and early detection, improvement in surgical management and postoperative care, implementation of and increased enrollment in clinical trials, focused research, and better understanding of the molecular mechanisms that make pancreatic cancer so aggressive and unresponsive to traditional treatment. It is only through continued clinical and translational research that meaningful progress will be made.

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