The Pathogenesis, Diagnosis, and Management of Pancreatic Cancer

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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; Review article; Presentation; Diagnosis; Management; Pathogenesis

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

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

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 epithelial tumors

Cystic neoplasms are less common than the ductal adenocarcinomas. They arise from the exocrine pancreas and are evenly distributed throughout the gland. Many pancreatic and peripancreatic cysts are actually benign inflammatory pseudocysts lacking epithelial lining. Differentiation between true cystic neoplasms and pseudocysts is imperative as their management varies greatly [41].

Serous Microcystic Adenomas (SMA) are epithelial neoplasms composed of uniform cuboidal glycogen-rich cells that usually form numerous small cysts containing serous fluid. These are more common in women with a 2:1 preponderance. SMAs can be located anywhere in the pancreas—head, body, or tail—and usually do not communicate with the pancreatic ducts [42]. Grossly, they appear as spongy, well-circumscribed, multiloculated cysts. Microscopically, they consist of a layer of simple cuboidal cells separated by dense 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 [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

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

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

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

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agent resulted in an improved outcome, with a 1.8-month improvement in both overall survival (HR 0.7, 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)

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