Cancer of the Pancreas

James H. North Jr., M.D., F.A.C.S.

It is estimated that in 2007, 37,170 patients will be diagnosed with cancer of the pancreas and 33,370 patients will die of this disease.[1] The highly lethal nature of this malignancy is largely related to the fact that most patients have advanced disease at the time of diagnosis. An increased awareness of the early signs and symptoms of cancer of the pancreas, coupled with a heightened clinical suspicion may improve our ability to identify this disease at an earlier stage. This would expand our therapeutic options and offer out patients a chance for better outcomes. For this reason, the pancreas was chosen as the tumor site for inclusion in this annual report.

The Carolinas Medical Center Northeast Experience

Methods

The Carolinas Medical Center Northeast (CMC-NE Tumor Registry was accessed for patients diagnosed with cancers arising in the pancreas from January 1999 to December 2006. Records were reviewed for clinical parameters such as age, gender, and tumor histology. All tumors were staged according to the 2002 American Joint Committee on Cancer criteria. (Table 1)[2]

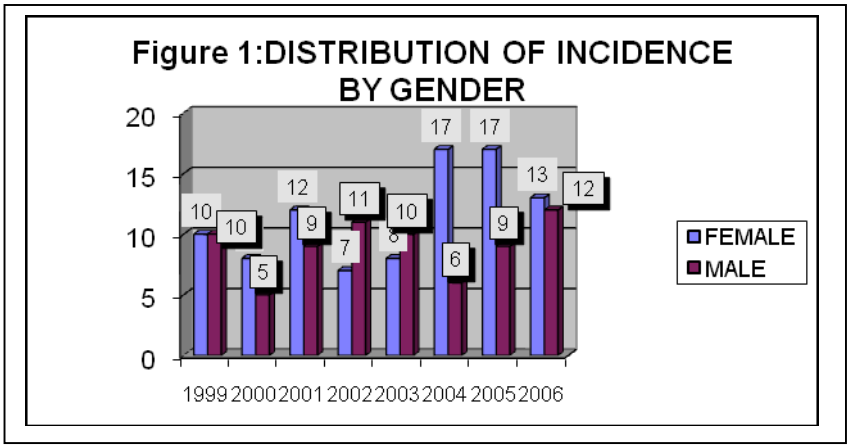
The types of treatment and patient outcomes were recorded. Disease specific survival was calculated according to the method of Kaplan and Meier.[3]

Table 1: American Joint Committee on Cancer Staging of Pancreatic Cancer

Primary Tumor (T)			
Tx	Primary tumor cannot be assessed		
T0	No evidence of the primary tumor		
Tis	Carcinoma in situ		
T1	Tumor limited to the pancreas ≤2cm in size		
T2	Tumor limited to the pancreas >2cm in size		
T3	Tumor extends beyond pancreas without SMA or celiac involvement		
T4	Tumor invades SMA or celiac		
Regional Nodes(N)			
Nx	Regional nodes cannot be assessed		
N0	No regional nodes		
N1	Regional nodal metastases		
Distant Metastases(M)			
Mx	Distant metastases cannot be assessed		
M0	No distant metastases		
M1	Distant metastases present		
Stage Grouping			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1 T2 T3	N1 N1 N1	M0 M0 M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Results

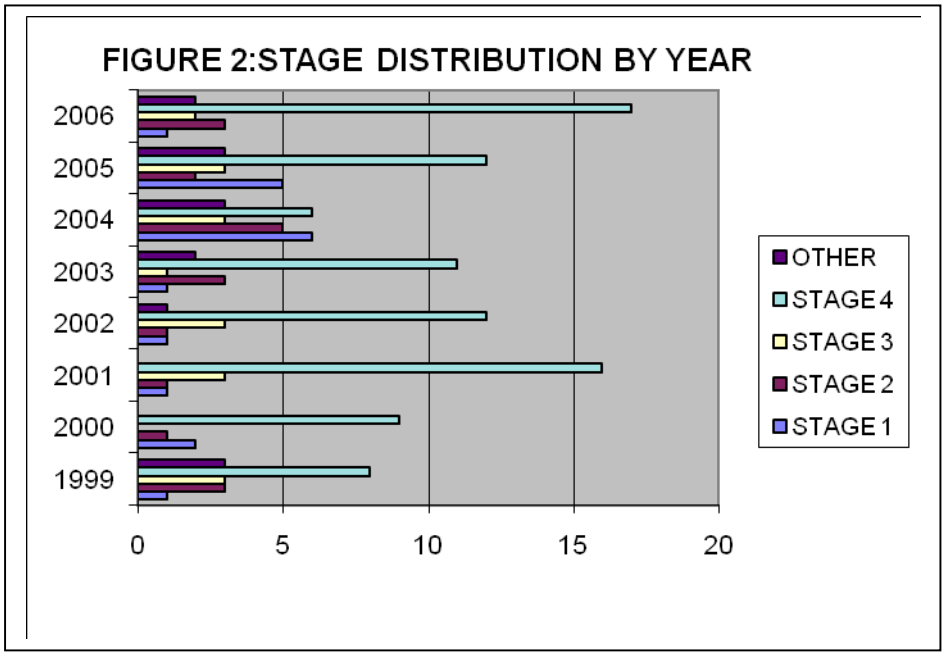
During the period January 1999 to December 2006, there were 164 patients diagnosed with pancreatic cancer. This included 92 women and 72 men. The gender distribution for each year of the study is shown in Figure 1.



The age at the time of diagnosis was grouped into decades. There was one patient diagnosed between the ages of 30 and 39 and four patients diagnosed in the 90-100 age group. The mode occurred in the 70 to 79 age group where 53 patients (32%) were diagnosed. Sixty-nine percent of cases were diagnosed between the ages of 50 and 79.

The stage distribution is depicted in Figure 2. Overall, there were 18 patients (11%) with Stage I disease, 19 patients (11.6%) with Stage II disease, 18 patients (11%) with Stage III disease, and 91 patients (55.5%) with Stage IV lesions. Staging information was incomplete for 18 patients (0.1%).

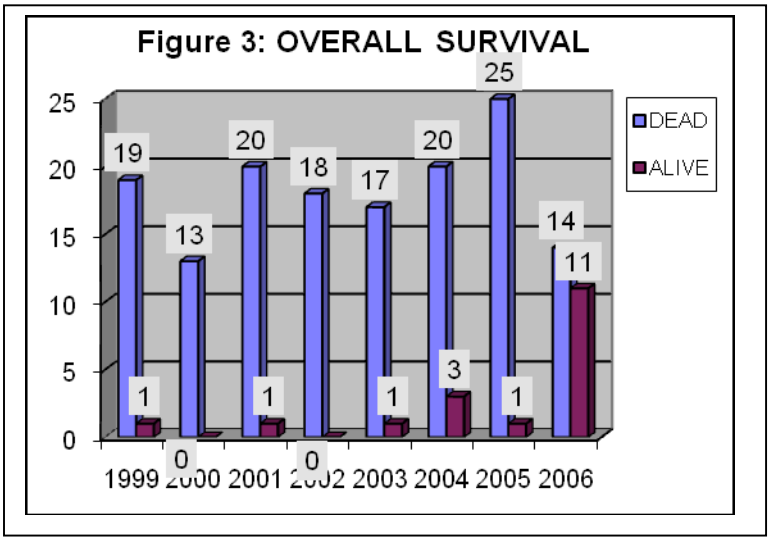
Cancer related treatment varied. The largest group of patients received palliative care only, (n=65, 36.5%). Forty-five patients (27.4%) received chemotherapy and 33 patients (20.1%) received a combination of chemotherapy and radiation. Nine patients (5.5%) received radiation alone. Only 11 patients underwent surgery. This included five patients who received surgery, chemotherapy and radiation, four patients who underwent surgery alone, and two patients who were treated with surgery and chemotherapy. One patient was treated with a combination of chemotherapy, radiation, and hormonal therapy.

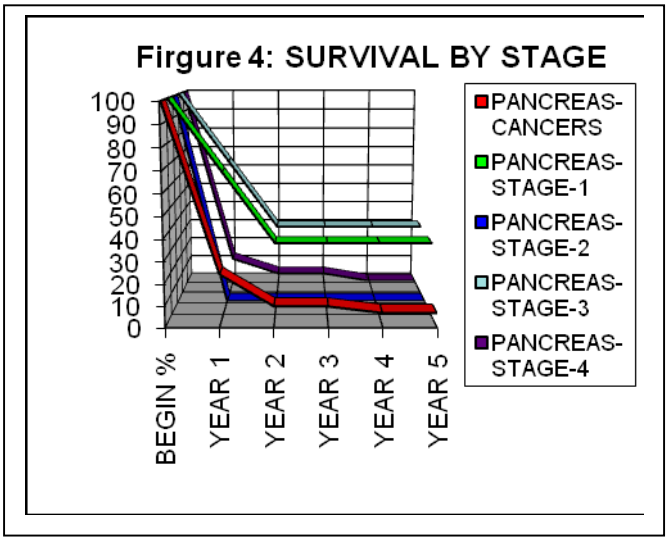


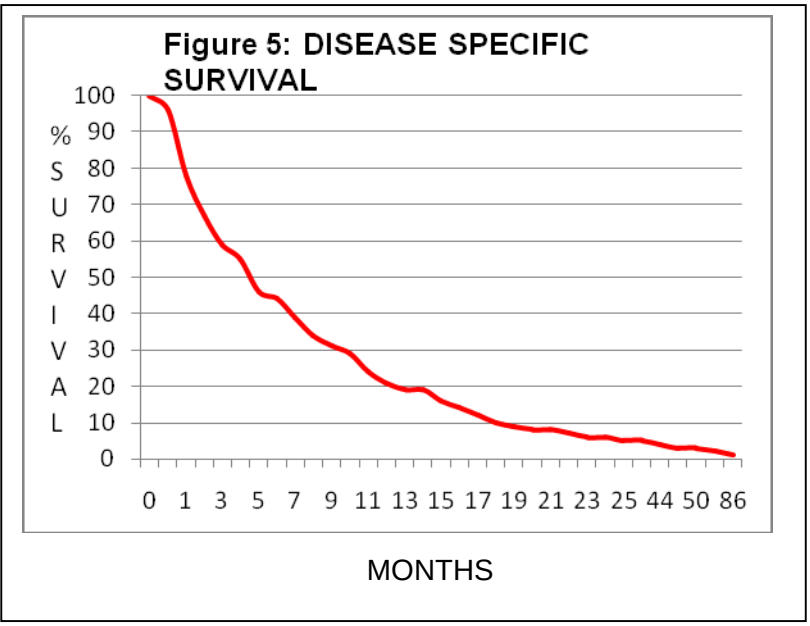
Survival ranged from 0 to 86 months. At the time of last contact, 18 patients (11%) were alive and 146 patients (89%) had expired. Overall survival is shown in Figure 3. Six of the expired patients had no evidence of cancer at their time of death. Six of the 18 living patients had no evidence of disease at last contact while 11 were alive with active cancer. Disease status was unknown for one patient. Survival by pathologic stage is demonstrated in Figure 4. As expected, survival was better in patients with Stage I disease. For patients with stage III tumors, a 30% survival was observed. This unexpectedly high survival may be a reflection of the limited sample size as well as the heterogeneous

nature of this tumor population which included all histologic types. Disease specific survival is shown in Figure 5.

.







Discussion

Cancer of the pancreas remains a lethal malignancy. This is largely due to the fact that most patients are not diagnosed until they have advanced or metastatic disease. At CMC-NE, fifty-five percent of the patients had distant metastases present at the time of diagnosis. This is very similar to the stage distribution reported by the Surveillance, Epidemiology, and End Results (SEER) Program where 51% of patients had distant disease. In this database, only eight percent of patients had localized disease. The overall 5-year relative survival rate for 1996-2003 from 17 SEER geographic areas was 5.0%.[4] This is similar to the 2.5% disease specific survival reported in this series.

The incidence of pancreatic cancer was found to increase with age. The majority of our cases occurred in the 50 to 79 year age group. Gold et.al. reported that 80% of cases of pancreatic cancer occur between the ages of 60 and 80. [5] This is similar to our experience. Pancreatic cancer has been reported to occur more frequently in males and the incidence and mortality rates among African Americans of both genders are higher than among Caucasians. [5] In our own series, there was a slight female predominance.

Diabetes mellitus and chronic pancreatitis have been implicated as factors which may predispose to the development of pancreatic malignancy. Tobacco and alcohol use have also been implicated. Some have also implicated coffee consumption as a risk factor but research has yielded conflicting results.[5] Genetic abnormalities have been identified in pancreatic tumors, leading investigators to implicate alterations in tumor suppressor genes in the development of pancreatic malignancies. Alterations in the tumor suppressor genes p53 and p16 have been recognized. In addition mutations in the oncogene, k-*ras*, have been discovered.[6] These genetic changes explain the development of pancreatic cancer in patients with familial pancreatic cancer, hereditary nonpolyposis colorectal cancer, familial atypical mole/melanoma, and BRCA2 associated familial breast cancer.

Many histoligic types of pancreatic neoplasms have been identified. Ductal adenocarcinoma is the most common and accounts for almost 75% of all non-endocrine pancreatic neoplasms. Serous cystadenocarcinoma and mucinous cystic neoplasms occur with less frequency. In addition, sarcomas and endocrine tumors can occur. Unfortunately, ductal adenocarcinomas, the most prevalent, are associated with the worst prognosis.

Clinical signs and symptoms of pancreatic cancer are often nonspecific and ignored. Worsening of diabetes as the gland becomes replaced by tumor is often a subtle finding. Commonly, patients present with jaundice due to a tumor in the pancreas causing an obstruction of the common bile duct. Abdominal or back pain is another presenting symptom. Clinical findings of endocrine tumors are related to the overproduction of hormones such as insulin or glucagon. Weight loss is a common problem among all patients with pancreatic cancer.

When a pancreatic tumor is suspected, imaging studies should be performed. Most commonly this involves a CT scan. This study is useful for excluding metastatic disease in the abdomen, identifying regional nodal involvement, and evaluating the extent of the primary tumor. The CT scan can identify involvement of the portal vein, which is not a contraindication to resection, or involvement of the superior mesenteric artery which does preclude surgical resection. Tumors in the head of the pancreas are sometimes evaluated with an endoscopic ultrasound. This device allows for further assessment of the local extent of the tumor as well as an examination of the regional nodes. A transduodenal fine needle aspiration biopsy of the pancreas may also be obtained with this device. The sensitivity of these biopsies is reported to be 78% and the specificity is as high as 100%.[7] The role of positron emission tomography (PET) remains controversial. The tumor markers, CEA and CA 19-9 should also be obtained. Prognosis is inversely related to the elevation of CA 19-9 when tumors express this antigen. Higher levels of CA 19-9 are usually associated with metastatic disease.

Endoscopic retrograde cholangiopancreatography (ERCP) is another useful procedure in the diagnosis of pancreatic tumors. This procedure may yield valuable information which supports the suspected diagnosis of pancreatic neoplasia. For example, obstruction of the common bile duct and the pancreatic duct, the "double duct sign" increases the suspicion of a pancreatic tumor. Brushings of the common bile duct may establish the presence of malignant cells. In addition, an ERCP can be therapeutic. Stenting of the common bile duct can provide palliation of biliary obstruction, through the use of temporary stents in patients who will undergo surgery or with permanent stents in patients who have unresectable disease.

In patients with a mass identified in the pancreas, a percutaneous biopsy is sometimes employed. This procedure is controversial. The yield of pancreatic biopsies is hindered by the degree of inflammatory changes that typically surround the tumor. In addition, there may be some risk of tumor seeding or bleeding complications with this type of biopsy. In patients who are surgical candidates, the establishment of a diagnosis prior to surgical intervention is generally not considered necessary. However, in patients who appear to have disease that is not amenable to resection, a percutaneous biopsy may be employed to confirm the diagnosis prior to starting chemotherapy or radiation.

Tumors that are confined to the pancreas and regional nodes are considered for surgical resection if they are medically fit. Involvement of the portal vein was considered a contraindication to resection in the past. However, more recent studies have demonstrated no reduction in survival when the vein is resected and reconstructed if necessary.[8] In some cases, laparoscopy may be employed prior to exploration to ensure the patient does not have distant metastases which have not been identified on preoperative imaging studies. While some advocate its routine use, more recently, this technology has been applied more selectively to patients with a higher risk of occult disease.[9]

Surgical therapy involves a resection of the involved portion of the pancreas. For tumors in the tail of the pancreas, this may involve a distal pancreatectomy. For lesions in the head, a pancreaticoduodenectomy (Whipple procedure) is usually employed. In many cases, a pylorus sparing pancreaticoduodenectomy, which avoids the antrectomy of a standard Whipple procedure, can be performed. For patients who are not candidates for surgery, either due to the extent of the tumor or for other medical reasons, chemotherapy, sometimes in combination with radiation, is utilized.

For patients who undergo resection, the role of adjuvant therapy remains controversial. The Gastrointestinal Tumor Study Group trial demonstrated improved survival with 5-fluorouracil (5-FU) and radiation after resection.[10] More current studies have questioned the incremental benefit of adjuvant therapy with 5-FU.[11] Gemcitabine has also been studied with promising results.[12] In general, all patients who undergo pancreatic resection should at least be considered for adjuvant therapy.

For patients with tumors that are not amenable to surgical resection, treatment with chemotherapy, often in combination with radiation is often employed. These patients may also benefit from focused radiation using the Cyberknife. The

management of patients with pancreatic malignancy should be discussed in a multidisciplinary forum to determine the best approach. In some cases, a period of neoadjuvant therapy may render some patients amenable to surgical resection.

Tumors of the pancreas remain a diagnostic and therapeutic challenge for the clinician. Critical opportunities exist to identify these patients at an earlier stage. Through multidisciplinary discussion and management, a diagnosis can be swiftly established and a treatment plan formulated. Through the continued efforts of all the healthcare professionals involved in the care of these patients, we can identify ways to improve outcomes in patients with this serious disease.

---

[1] Jemal A, Siegel R, Ward E, et. Al. Cancer statistics 2007, CA Cancer J Clin 2007;57:43–66.

[2] American Joint Committee on Cancer. Cancer Staging Manual 6th ed. Springer, New York, NY 2002, 179-188.

[3] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53: 457-468.

[4] Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 17 Regs Limited-Use, Nov 2006 Sub (1973-2004 varying), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2007, based on the November 2006 submission.

[5] Gold E, Goldin S.:67-91. Epidemiology and risk factors for pancreatic cancer. Surg Oncol Clin NA 1998;7:67-91.

[6] Hruban RH, Petersen GM, Ha PK, Kern SE. Genetics of pancreatic cancer from genes to families. Surg Oncol Clin NA 1998;7:1-23.

[7] Duffy JP, Reber HA. Pancreatic Neoplasms. Curr Opinions in Gastroenterol 2003;19:458-466.

[8] Tseng JF, Raut CP, Lee JE, etal. Pancreaticoduodenectomy with vascular resection:margin status and survival duration. J Gastrointest Surg 2004;8:949-950.

[9] Stefanidis D, Grove K, Schwesinger WH, Thomas CR. The current role of staging laparoscopy for adenocarcinoma of the pancreas:a review. Ann Surg Oncol 2006;17:189-199.

[10] Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg 1985;120:899–903.

[11] Neoptolemos jp, Stocken DD, Friess H, etal. ESPAC-1: Final Results of a European, randomized controlled trial to assess the roles of adjuvant chemotherapy and adjuvant chemoradiation in resectable pancreatic cancer. Pancreatology 2003;3:209–269.

[12] Regine WF, Winter KW, Abrams RA, et al. RTOG 9704 a phase III study of adjuvant pre and post chemoradiation (CRT) 5-FU vs. gemcitabine (G) for resected pancreatic adenocarcinoma. J Clin Oncol 2006; 24(suppl 1) 4007.