# PANCREATIC ADENOCARCINOMA

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# ADENOCARCINOMA OF THE PANCREAS

In the USA, pancreatic cancer ranks as the fourth most common cause of cancer death in men (after lung, colon and prostate) and the fifth most common in women (after lung, breast, colon and ovary-uterus) (Table 1).

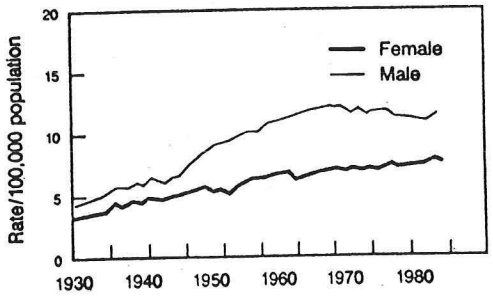
**Table 1**
**Death due to cancer in the USA**

| Men | Women |
|---|---|
| Lung | Lung |
| Colon | Breast |
| Prostate | Colon |
| **Pancreas** | Uterus/ovary |
| | **Pancreas** |

Pancreatic cancer also has the distinction of having the lowest five-year survival rate of all cancers.[1-3] In one series with approximately 15,000 patients, there were only 65 5-year survivors (0.4%).[4] Forty percent of patients diagnosed of pancreatic cancer will be dead within 4 months, 65% within 6 months and about 90% at 1 year.[4]

## Incidence

It is estimated that pancreatic cancer is the cause of death in over 25,000 Americans per year.[3,5,6] For unknown reasons, the incidence of pancreatic cancer in the USA has increased from less than 5 per 100,000 in 1935 to 11-12 per 100,000 in 1985 in men and slightly less for women (Figure 1).[7]




*Adjusted 1970 U.S. Census

FIGURE 90-1. Age-adjusted pancreatic cancer death rates for selected sites for females and males 1930-1985. (Adapted from Silverberg E, Lubera JA. Cancer statistics 1988. Ca 1988;38:5.)

While in some industrialized countries such as Sweden, the incidence of pancreatic carcinoma has remained stable at 12.5 per 100,000.[8] Other countries such as Japan have also experienced an increase in the incidence of pancreatic cancer from 1.8/100,000 in 1960 to 5.2/100,000 in 1985.[9] In contrast, third world countries such as India, Kuwait and Singapore have a low incidence of pancreatic cancer (2.2 per 100,000).[10]

**Demographics** Pancreatic cancer is rare in subjects younger than 40 years old. About 80% of patients with pancreatic cancer are between 60 and 80 years old.[2] Pancreatic cancer is more common in men than in women with a ratio of 1.3/1, and is more common in urban than in rural areas. For unclear reasons, blacks in the USA, native Polynesians in Hawaii, Maoris in New Zealand and urban dwellers around the world appear to have a higher incidence of

pancreatic cancer.[5,11,12] Blacks throughout the USA have incidence rates 1.5 to 2.0 times those of whites except in Connecticut where the incidence rate for both black and white men is 8.0 per 100,000.[13] The high rate of pancreatic cancer in blacks in the USA is not paralleled in African populations, suggesting important environmental factors.[13] Neither income nor education has any effect on the risk of developing pancreatic cancer.[12,14-16]

**Associations**

**Tobacco** The best established risk factor for pancreatic cancer is smoking. In several case-control and cohort studies, the relative risk for cigarette smokers compared with non-smokers ranged from 1.4 to 2.3.[17-24] There is a modest direct correlation between smoking and the risk for pancreatic cancer.[9,23] The risk levels off 10-15 years after cessation of smoking.[23] In contrast to cigarettes, other tobacco products have not been associated with an increased risk for pancreatic cancer.[16,23,25,26] However, Wynder et al found a two-fold increased risk associated with pipe and cigar smoking.[27] Experimentally, pancreatic tumors can be induced in animals by life long administration of tobacco-specific nitrosamines in drinking water.[28]

The mechanism by which tobacco promotes pancreatic cancer has not been established. It is possible that inhaled carcinogens may reach the pancreas through the bloodstream or inactive carcinogen precursors may be activated in the liver, excreted into bile and then refluxed into the pancreatic duct.[17,29]

**Alcohol** Previous studies have reported that alcohol use predisposed to pancreatic cancer.[30-32] However, recent studies found no link between alcohol consumption and the risk for development of pancreatic cancer.[17,18,21,22,24,25,27,33-37] Furthermore, some papers found that moderate consumption of wine and beer had slight protective effects on the risk of developing pancreatic cancer.[21,22,33]

**Coffee** In 1981, McMahon et al generated much public and scientific concern with a report that coffee consumption was associated with pancreatic cancer and that there was a dose response relationship ($p<0.001$).[18] This finding was later supported by another study.[33] However, these data has been challenged by numerous papers that found no association between coffee consumption and pancreatic cancer.[21,22,24,31,36,38-43]

In summary, there is no apparent association between alcohol or coffee consumption and pancreatic cancer.

**Diet** Some studies have found a positive correlation between per capita ingestion of fats, meat and pancreatic cancer.[9,30,35,44-46] In addition, a high fat diet acts as a tumor promoter in animal models of pancreatic carcinogenesis.[47-50] Other papers have not found an association with fat intake and pancreatic cancer [44,51] but with high caloric intake [51] or high protein consumption.[44] In contrast, high intake of fruits and vegetables appears to have a

protective effect against pancreatic cancer.[23,33,35,45,51,52] It has been proposed that the protective effects of fruits and vegetables may be related to the protease inhibitor contents of these foods. Protease inhibitors may block the formation of oxygen radicals, by preventing digestion of proteins to the amino acids needed by rapidly dividing cancer cells, or by inhibiting poly(ADP-ribose) formation and thereby reducing DNA damage.[12] The protective effect may also be related to their protease inhibitor content or to their ascorbic acid or ß-carotene content, both of which have known anticarcinogenic effects.[12]

**Diabetes** Patients with diabetes have a 2-3 fold risk for developing pancreatic cancer.[17,24,36,45,53,54] Experimentally-induced diabetes appears to enhance the growth of pancreatic cancer.[55]

**Partial Gastrectomy** Patients with partial gastrectomy have 3 to 7 times greater risk for developing pancreatic cancer.[19,56] It has been proposed that increased formation of N-nitroso compounds by nitrate reductase producing bacteria that proliferate in the hypoacidic stomach could be responsible for both gastric and pancreatic cancers. It is also possible that altered gastric regulation of pancreatic function as a result of partial gastrectomy may affect the homeostatic responses to pancreatic toxins and thereby increase the risk.[57]

**Pancreatitis** Chronic pancreatitis has been associated with pancreatic cancer in historical, clinical, and autopsy studies.[58-61] However, case-control studies have not reported an association between chronic pancreatitis and pancreatic cancer.[19,33,62] At this point a true association between chronic pancreatitis and pancreatic cancer should be confined to hereditary and tropical pancreatitis.[63-65]

**Occupation, industry and related exposures** One study reported that white men employed in the manufacture of 2-naphthylamine and benzidine who were followed for 25 years had a five-fold increase in the risk and mortality from pancreatic cancer.[66] Other studies have found an increased risk of pancreatic cancer for members of the Chemical Society,[14,67] commercial pressmen,[68] and workers in dry cleaning industries,[69] petrochemical plants,[70,71] and oil refineries.[69,71,72] However, these studies failed to isolate a particular carcinogen or class of carcinogens responsible for the modest risk involved in working in these institutions.

**Radiation** The effect of radiation in promoting pancreatic cancer is controversial. Workers exposed to radiation in atomic plants,[73,74] and patients who received radiation therapy for ankylosing spondylitis [75] appear to have an increased risk for pancreatic cancer. However, Japanese survivors of the atomic bomb do not have increased rates of pancreatic cancer [76] and in a British study, workers in an atomic plant did not have an excess of pancreatic cancer.[77]

**Pernicious anemia** One report from Sweden claimed an increased incidence of pancreatic cancer in patients with pernicious anemia.[78] The validity of this study awaits confirmation.

**Protective conditions** Some studies have suggested that allergic disease [19,33,36,62] and tonsillectomy [21,33,45] have a protective effect of against pancreatic cancer.

**Pathology and anatomical considerations**

There are a large number of morphologic varieties of primary pancreatic carcinoma (Table 2). However, ductal adenocarcinomas make up to 92% of pancreatic neoplasms.[79-81]

**Table 2**
**Primary malignant Neoplasms of the nonendocrine pancreas**

**Duct cell origin (88.8%)** Duct cell carcinoma, Giant cell carcinoma, Adenosquamous carcinoma, Mucinous carcinoma, Microadenocarcinoma, Cystoadenocarcinoma, Papillary cystic tumor, Intraductal papillary neoplasm, Oat cell carcinoma, Carcinoid,
**Acinar cell origin (1.2%)** Acinar cell carcinoma, Acinar cell cystoadenocarcinoma
**Mixed cell type (0.2%)** Duct-islet cell, Duct-islet-acinar cell, Acinar-islet cell, Carcinoid-islet cell
**Connective tissue origin (0.6%)** Leiomyosarcoma, Fibrosarcoma, Histiocytoma, Lymphoma, Hemangiopericytoma, Rhabdomyosarcoma
**Uncertain histogenesis (9.2%)** Pancreaticoblastoma, Unclassified (large, small and clear cell)

From reference [79]

From the anatomical point of view, the pancreas lacks a mesentery, lies adjacent to the common bile duct and other vital porta hepatis structures, and is surrounded by the duodenum, stomach and colon (Fig 2).

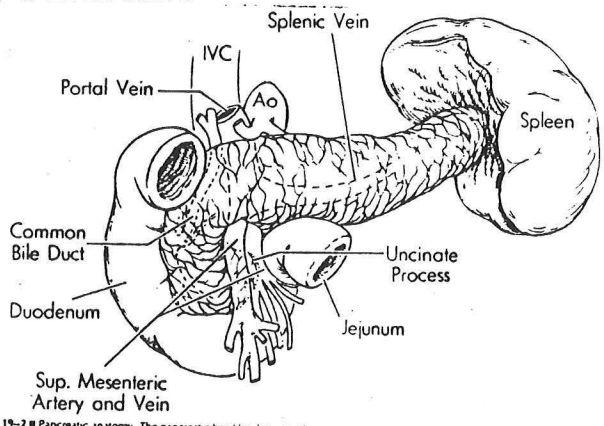



FIGURE 19–2 ■ Pancreatic anatomy. The pancreatic head lies between the superior mesenteric vessels and the second portion of the duodenum. The uncinate process lies behind the mesenteric vessels, and the neck lies ventral to them. The body lies ventral to the splenic vein. The tail constitutes the last few centimeters of the gland, lies intraperitoneally, and inserts into the splenic hilum within the leaves of the splenorenal ligament.

About 60-80% of pancreatic tumors are located in the head of the pancreas,[47,79,82] and most arise from the dorsal pancreas close to the intrapancreatic portion of the common bile duct.[83] The remaining tumors in the head of the pancreas arise in the central pancreatic head behind the ampulla of Vater or the uncinate process close to the ventral pancreatic duct. Initial clinical manifestations are associated with the location of the tumor. Tumors that arise from the dorsal pancreas rapidly obstruct the distal common bile duct and produce obstructive jaundice. Tumors

Tumors arising near the ampulla of Vater or uncinate process tend to obstruct the main pancreatic duct and cause pancreatic insufficiency and obstructive pancreatitis. Tumors of the head of the pancreas are relatively large when first diagnosed. At the time of diagnosis 85% of tumors have extended beyond the organ.[81] Tumors of the body and tail of the pancreas are detected later and are even larger in diameter (5-7 cm) than tumors in the head of the pancreas (2.5-3.5 cm).[84]

Pancreatic adenocarcinoma extends to the retroperitoneal spaces behind the pancreas, envelops and fixes vessels. It invades peripancreatic fat, tends to invade the nerves within and beyond the gland and spreads locally and metastasizes early through lymphatic spread.[81,85] The most common sites of extralymphatic involvement are the liver and peritoneum and the lung is the most frequently affected extraabdominal organ.[81] In advanced cases the tumor invades the duodenum, stomach and gallbladder. Tumors in the tail of the pancreas also invade the spleen, the splenic vein and left adrenal gland.

**Experimental Models of Pancreatic Cancer**

Experimental models of carcinogenesis of the exocrine pancreas employ Syrian Hamsters [86,87] and rats.[88,89] An interesting difference between the two species is that tumors induced in the Hamster are of the ductal type (similar to human adenocarcinoma) while in the rat the tumors primarily involve the acinar cells.[90,91] Pancreatic ductal adenocarcinoma in hamsters originates in all branches of the pancreatic ducts. It is induced by N-nitrosobis (2-oxopropylamine or BOP) or other N-nitrosamines arising from ß-oxidation of N-nitrosodipropylamine.[91] In the rat model, acinar cells are more susceptible to carcinogenesis. The common chemical inducer is azaserine (Table 3).[89,92]

**Table 3**
**Animal models of pancreatic carcinogenesis**

| MODEL | AGENT | TYPE OF CANCER |
|---|---|---|
| Hamster | N-nitrosobis | Ductal |
| Rat | Azaserine | Acinar |

Pancreatic cancer can also be produced by transgenic techniques in mice. However, these tumors are primarily of the acinar type.[93,94]

**Cytogenetic and genetic alterations in pancreatic cancer**

The evidence for a genetic component for the etiology of pancreatic cancer comes from: 1) isolated familial clusters of pancreatic cancer, 2) the occurrence of pancreatic cancer in several heritable syndromes and 3) studies showing both numerical and structural chromosome abnormalities.[95]. However, no study has been able to determine a specific genetic element unique to, or essential for pancreatic tumorigenesis.

**Alteration in oncogenes and growth regulatory peptides** Human cancer arises from an accumulation of genetic derangements within the cell, accompanied by a progressive loss of growth regulation. Genetic mutations involved in neoplastic formation involve two classes of genes, the proto-oncogenes and the tumor-suppressor genes.[96] **Proto-oncogenes** encode proteins that regulate cell growth and proliferation. Oncogenes act dominantly as mutation of one allele is sufficient to promote tumor formation. The most common oncogenes in human cancers are the *ras* gene family, including K-*ras*, H-*ras* and N-*ras*.[96] The *ras* gene is converted to active oncogene by point mutations occurring in either codon 12, 13 or 61. Human pancreatic cancers are associated with an activating mutation of K-*ras* proto-oncogene in over 90% of cases. In the majority of cases the mutations are located in codon 12.[95-99] A similar mutation has been reported in carcinogen-induced hamster pancreatic ductal carcinoma.[100,101] Proteins encoded by proto-oncogenes include growth factors, growth factor receptors, and regulators of transcription and signal transduction.[96] Epidermal Growth factor (EGF) has been shown to promote pancreatic carcinogenesis in hamsters.[102,103] In human pancreatic carcinoma cell lines, several growth factor alterations have been demonstrated. These include: 1) overexpresion of EGF, and transforming growth factor $\alpha$ (TGF$\alpha$).[95,104-106] and 2) increased expression of the epidermal growth factor receptor (EGF-R) which appears to be a result of structural and/or numerical aberration of chromosome 7p.[107]

TGF$\alpha$ is 10-100 times more potent than EGF in stimulating anchorage independent growth. It binds to the EGF receptor and does not downregulate the expression of the receptor as occurs normally with EGF.[108-110] Thus, it may lead to uncontrolled autocrine growth.

Molecular biological techniques to determine K-ras gene mutations may prove useful in the differential diagnosis of pancreatic masses. A mentioned above, K-ras mutations have been determined in small tissue samples of pancreatic cancers.[97,98] K-ras mutations seem to be quite specific for pancreatic cancer with no overlap with chronic pancreatitis, normal pancreas or other midabdominal tumors (Table 4).[97] It is possible that fine needle aspirates may be all the tissue needed to confirm a diagnosis.

**Table 4**
**Analysis of K-*ras* gene mutations at codon 12 in tissues obtained from surgery or autopsy**

| | No. of cases | No. of cases with mutation |
|---|---|---|
| Pancreatic adenocarcinoma | 18 | 18 (100%) |
| Insulinoma | 2 | 0 |
| Chronic pancreatitis | 9 | 0 |
| Normal pancreas | 16 | 0 |
| Extrahepatic bile duct Ca | 12 | 1 (8%) |
| Gallbladder Ca | 11 | 0 |

Adapted from reference [97]

**Tumor suppressor genes or anti-oncogenes** This gene family inhibits oncogenes and cellular growth and proliferation. Normally, two alleles, one maternal and one paternal, are inherited for a given gene. In contrast to proto-oncogenes, the loss of one of the suppressor alleles is well tolerated by the cell. Loss of the second allele deletes the gene, removing its growth suppression activity and contributing to tumor formation.[96] A large number of tumor suppressor genes have been identified. However, the p53 gene is the most frequently mutated gene known to human tumorigenesis.[96,111,112] The precise mechanism of action or biochemical functions of the p53 gene remains to be explained. However, allelic deletions of human chromosome 17p (the p53 gene locus) and mutation or deletion of the p53 gene have been observed in a variety of human malignancies.[111,112] Recent studies by Ruggeri et al [95] and Barton et al [113] have found p53 abnormalities in human pancreatic tumors and tumor-derived cell lines. It is possible that alteration in suppressor genes may complement and enhance the tumor promoting effect of K-*ras* activation.

## Pancreatic cancer and hormones

**Cholecystokinin (CCK)** CCK stimulates pancreatic enzyme secretion and growth in the normal pancreas.[114-116] The evidence for a role of CCK in pancreatic carcinogenesis comes from the presence of CCK receptors in pancreatic tumors,[117-119] the enhancement of tumor formation with administration of exogenous CCK,[120,121] and the inhibition of this effect by the use of CCK receptor antagonists.[122-124]

In experimental models of pancreatic carcinogenesis, CCK has been found to stimulate the development and increase the frequency of tumors in hamsters.[120] CCK also shortens the latency to preneoplastic lesions in rats,[121] and the use of a CCK receptor antagonist can prevent this effect.[123] However, the effect of CCK on animal models of pancreatic carcinogenesis is controversial. In the hamster model, exogenous administration of CCK simultaneously or shortly before the carcinogen N-nitrosobis inhibited cancer induction.[125,126] CCK has also been shown to stimulate growth in some [119,127,128] but not all [129] cell lines of human pancreatic cancer. In some studies CCK antagonists inhibit pancreatic cancer growth. In the azaserine-induced pancreatic cancer in the rat, CR-1049, a CCK antagonist, inhibits the effect of exogenous CCK.[123] Other selective CCK antagonist also inhibit the growth of human pancreatic cancer cell line.[124]

**Bombesin** Bombesin, a member of the gastrin releasing peptide hormones family, promotes pancreatic growth [130] and promotes the growth of azaserine-induced pancreatic acinar tumors.[123] However, chronic treatment with bombesin inhibits the growth of human pancreatic cancer in nude mice.[131]

**Vasoactive intestinal peptide (VIP)** VIP receptors have been found in both normal and neoplastic pancreatic tissue.[132,133] Chronic VIP treatment inhibits the growth of hamster pancreatic cancer but not human pancreatic cancer.[134]

**Somatostatin** Somatostatin has been shown to inhibit the growth of pancreatic cancer in experimental models in rats, hamsters and nude mice.[135,136] Somatostatin prolongs tumor doubling time [136] and appears to produce cell death in carcinogen-induced pancreatic cancer in hamsters.[137] The effect of somatostatin may be due to a directly mediated response, [138,139] and/or by inhibition of other hormones such as CCK which may promote tumor growth.[140]

**Glucocorticosteroids and sex hormones** Both estrogen and androgen receptors have been found in normal [141-143] and neoplastic pancreatic tissue.[142,144-146] Estrogens seem to have a protective effect against pancreatic cancer growth. It is more difficult to induce pancreatic cancers using azaserine in female rats that it is in male rats, and this protection disappears with prior oophorectomy and tamoxifen treatment.[147] Estrogen treatment and castration also inhibit the early stages of acinar pancreatic carcinogenesis after azaserine treatment in male rats.[148] In contrast, androgens seem to have a trophic effect on human pancreatic cancer in nude mice and tissue culture.[149-153] Glucocorticoids also seem to stimulate pancreatic cancer growth.[115,152]

## Clinical Presentation

Pancreatic cancer usually produces non specific signs and symptoms early in the course of the disease.

**Pain** Patients usually complain of vague, dull, constant, poorly localized, upper abdominal pain, sometimes with radiation to the back. Rarely the pain may be located in the lower abdomen.[154] Unfortunately, pain usually implies direct invasion of adjacent retroperitoneal organs or splanchnic nerves and predicts advanced disease.[155] Pain occurs during the course of pancreatic cancer in up to 90% of cases [154] and is the presenting symptom in 79% of patients.[156] Abdominal pain may precede jaundice for up to 3 months.[157]

**Jaundice** Is the first manifestation in 80-90% of patients with carcinoma of the head of the pancreas and in 6-13% of patients with carcinoma of the body and tail of the pancreas.[79,158,159] Jaundice in patients with cancer in the head of the pancreas is due to compression of the distal common bile duct. Patients with tumors in the body and tail may become jaundiced as a result of hepatic metastasis or obstruction at the porta hepatis by lymphadenopathy.

**Other symptoms** Non specific constitutional symptoms as anorexia, weight loss and weakness are common. Weight loss of more than 10% of ideal body weight is seen in most patients with pancreatic cancer [79,160,161] and predicts advanced disease.[155,162] The weight

loss is usually due to malabsorption, poor calorie intake or a combination of both.[161] It is presumed that malabsorption is due to pancreatic duct obstruction and reduced pancreatic secretion.[163]

Diabetes may be present in up to 68% and glucose intolerance may be seen in as many as 81% of patients with pancreatic cancer.[54,79,164-167] However, polydipsia, polyuria and hyperphagia are rare presenting features.

In rare cases, acute pancreatitis may be the first manifestation of pancreatic cancer.[168,169]

It is of interest that in a recent review of the literature depression and or anxiety was present in 50% of patients with pancreatic cancer before the diagnosis was made.[170]

Other symptoms are summarized in Table 5.

**Table 5**

**Presenting Features of Pancreatic Cancer**

| HEAD | | BODY AND TAIL | |
|---|---|---|---|
| Feature | % patients | Feature | % patients |
| Weight loss | 92 | Weight loss | 100 |
| Jaundice | 82 | Pain | 87 |
| Pain | 72 | Weakness | 43 |
| Anorexia | 64 | Nausea | 43 |
| Dark urine | 63 | Vomiting | 37 |
| Light stools | 62 | Anorexia | 33 |
| Nausea | 45 | Constipation | 27 |
| Vomiting | 37 | Food intolerance | 7 |
| Weakness | 35 | Jaundice | 7 |
| Pruritus | 24 | | |

From reference [79]

**Physical findings** Cancer in the head of the pancreas presents with jaundice and hepatomegaly in up to 80% of cases.[79,82,171] In contrast, cancer in the body and tail present with hepatomegaly and jaundice in less than 30% of cases.[79,82,172] A palpable gallbladder (Courvoisier's law) is present in up to 30% of patients with cancer in the head of the pancreas.[79,82,172] Patients with cancer in the body and tail may present with ascites.[79,82,172] A palpable mass and peripheral edema may be seen in up to 20% of cases.[79,82,172] Thromboembolism or Trousseau's sign can also be seen.

## Diagnosis

Most patients with pancreatic cancer are diagnosed on the basis of advanced symptoms, at which time most tumors are unresectable.

**Serum studies** Routine serum laboratory examinations are not specific. Elevation of the alkaline phosphatase is commonly seen from either bile duct obstruction or hepatic metastasis.[5,173] Elevation of serum amylase and or lipase is uncommon, and is not specific for pancreatic cancer it may be seen in benign pancreatic diseases and other tumors.[173]

**Tumor markers in serum** A large number of tumor markers have been studied for the diagnosis of pancreatic cancer. These include tumor-associated antigens, enzymes [174-176] and hormones.[177,178] The review of all tumor markers is beyond the scope of this review. We will focus in the most widely used tumor markers.

**Carcinoembryonic antigen (CEA)** CEA has been found to be elevated in 50-70% of patients with pancreatic cancer.[174,179,180] However, this tumor marker is not specific for pancreatic cancer and is found in different gastrointestinal tumors. Currently it is used for follow up of patients with colorectal carcinoma.

**Carbohydrate antigen CA 19-9** This tumor marker was isolated by Koprowski et al as a monoclonal antibody from a human colon cancer cell line.[181,182] This was followed by the development of a simple radioimmunometric assay to measure CA 19-9 by DelVillano et al.[183] The oligosaccharide on which the CA 19-9 epitope is found is sialylated Lewis A blood group antigen. Five percent of the general population who are genotypically Lewis a and b negative can not synthesize CA 19-9. [184-186] This is why the maximum achievable sensitivity with CA 19-9 for the diagnosis of pancreatic cancer is 95%.[186,187] False positive elevations of CA 19-9 have been reported in patients with benign disease such as chronic pancreatitis,[187,188] fulminant hepatic failure,[189] cirrhosis,[187,190-192] and bile duct obstruction with acute cholangitis.[193] Elevated CA 19-9 blood levels can be seen in up to 62% of patients with cirrhosis and in some cases the elevation was greater than 100 U/ml.[190,194] Acute cholangitis has been associated with CA 19-9 blood levels over 1000 U/ml. These levels return to normal after bile duct decompression.[193,194] Increased blood CA 19-9 levels can also be seen in other gastrointestinal malignancies (Table 6).[187,192,195]

**Table 6**
**Conditions associated with elevated CA 19-9**

1. Pancreatic Adenocarcinoma
2. Other GI malignancies
   - Stomach
   - Hepatobiliary tree
   - Colon
3. Benign disease
   - Chronic pancreatitis
   - Fulminant hepatic failure
   - Cirrhosis
   - Cholangitis

CA 19-9 is not a good screening test. Frebourg et al [194] measured CA 19-9 in 866 patients admitted to a hospital, CA 19-9 level was increased in 117 patients and only one patient was found to have a pancreatic cancer. Using 37 U/ml as the upper limit of normal, CA 19-9 has a mean sensitivity and specificity of 81% and

90% respectively.[187,196] Increasing the cutoff from 37 U/ml to 1000 U/ml decreases the sensitivity but increases the specificity to over 99%. This translates to a better predictive values (Table 7).

**Table 7**
**Predictive value of CA 19-9 for the diagnosis of pancreatic cancer**
**Predictive value of CA 19-9**

| Cutoff (U/ml) | Positive predictive value | Negative predictive value |
|---|---|---|
| 37 | 72.3 | 95.8 |
| 100 | 87.2 | 93.8 |
| 300 | 92.0 | 91.3 |
| 1000 | 97.2 | 89.2 |

From reference [187]

The sensitivity of CA 19-9 is also associated with the size of the tumor, the larger the tumor, the greater the sensitivity. Small tumors, defined as less than 3 cm are associated with elevated CA 19-9 levels in about 50% of cases.[187,197-200] However, one study that specifically looked at small pancreatic tumors, found that only 30% of patients had CA 19-9 values greater than 37 U/ml,[201] indicating that CA 19-9 may not be helpful for early diagnosis.[187]

CA 19-9 levels have been correlated with tumor resectability. Only 4% of patients with CA 19-9 levels above 1000 U/ml will have resectable tumors (Table 8).[187,196,197,199,202,203]

**Table 8**
**Levels of CA 19-9 and unresectability**

| Author | # Resectable patients CA 19-9 > 1000 | # Resectable patients CA 19-9 < 1000 |
|---|---|---|
| Schmiegel | 2/3 | 16/37 |
| Satake | 0/2 | 2/7 |
| Steinberg | 1/14 | 9/23 |
| Safi | 0/3 | 8/45 |
| Favero | 0/3 | 1/26 |
| Wang | 0/3 | 14/21 |
| Malesci | 0/16 | 22/45 |
| Total | 3/44 (6.8%) | 72/204 (35%) |

From reference [187]

Patients whose CA 19-9 falls to normal range after tumor resection appear to have a better prognosis than patients who do not normalize CA 19-9 levels.[204-206] Mean survival in patients who normalized CA 19-9 levels postoperatively was 17 and 18 months.[204,205] In contrast, none of the patients who did not normalize CA 19-9 levels lived more than 7 months.[187,204,205] CA 19-9 has also been used to detect pancreatic cancer recurrences before disease becomes clinically or radiologically evident.[204-206] The cost-effectiveness of CA 19-9 has been analyzed by Richter et al.[207] The authors compared two comprehensive diagnostic strategies, one beginning with CA 19-9 and the other beginning with ultrasonography. They concluded that CA 19-9 was a useful and cost effective initial test in the evaluation of suspected pancreatic cancer. However, a recent prospective study concluded that the best use of CA 19-9 was to confirm pancreatic imaging procedures in patients with strong clinical suspicion of pancreatic malignancy.[192]

In summary, CA 19-9 is not tumor specific and should not be performed in the asymptomatic population. The exact role for CA 19-9 in the evaluation and screening of patients with suspected pancreatic cancer is yet to be determined. However, it appears to be of value in evaluating patients with jaundice, abdominal pain and weight loss. Ca 19-9 may predict resectability, define postoperative prognosis and help in the early recognition of postoperative recurrences.

**Imaging Studies**

The definition of pancreatic anatomy with ultrasonography (US) or computed tomography (CT) is the cornerstone for the diagnosis of pancreatic cancer. These imaging techniques can also determine: a) dilation of the biliary and/or pancreatic ducts, b) extrapancreatic spread of the tumor, c) vascular involvement and d) metastasis.

**US** is a noninvasive and inexpensive imaging test that is commonly used in the evaluation of jaundice. However, the success and accuracy of the examination is dependent on the skill of the operator and body habitus of the patient. Incomplete or inadequate visualization of the pancreas can occur in 13% to 38% of examinations.[208-210] In experienced centers US has a high sensitivity and specificity for diagnosing pancreatic cancer. In a review of several studies by Niederau et al, US had a sensitivity of 76% and a specificity of 90% for the diagnosis of pancreatic cancer.[211] US has not proven to be very useful for staging and assessing resectability of pancreatic tumors.[211]

**CT** is also noninvasive, allows complete examination of the pancreatic gland in most patients, and does not rely as much in operator skill and body habitus when compared to US. However, CT is expensive and exposes the patient to ionizing radiation. In the review by Niederau et al,[211] the sensitivity and specificity of CT for diagnosing pancreatic cancer were 83% and over 90% respectively. An advantage of CT over US is that it is useful to

determine staging and assess resectability. In the USA most institutions favor CT over US.[212,213]

**Magnetic resonance imaging (MRI)** MRI can characterize pancreatic tumors and is capable of differentiating between normal pancreas and tumor.[214,215] In earlier studies it appeared that MRI had no significant advantage over CT.[214] However, in a recent prospective study MRI was superior to CT in the identification of pancreatic tumors, in particular small tumors.[215] Contrast agents for MRI are being studied to increase the sensitivity and specificity for the diagnosis of pancreatic cancer.[216] Further studies are required to determine the accuracy and clinical value of MRI in the diagnosis of pancreatic cancer.

**Endoscopic retrograde cholangiopancreatography (ERCP)** ERCP is an invasive procedure that can confirm the diagnosis of pancreatic cancer and reveal extension of tumor into the duodenum. Both the sensitivity and specificity of ERCP in the diagnosis of pancreatic cancer are over 90% .[174,211,217] In one study, the pancreatogram was normal in only 3% of patients with pancreatic cancer.[218]

In contrast with US, CT and MRI, ERCP is associated with a small but significant risk of complications (bleeding, perforation, pancreatitis).[219] As in the case of other imaging techniques, ERCP can not definitely distinguish benign from malignant. In an attempt to increase the diagnostic yield, cytology specimens can be obtained at the time of ERCP. In one study, pancreatic juice was obtained during cannulation of the pancreatic duct, and positive cytology was present in 76% of patients with pancreatic cancer.[220] The use of a special brush to obtain exfoliative cytology has also been described.[221,222]

In summary, ERCP and imaging studies such as US and CT are not competitive but complementary.[223] In some cases a positive cytology obtained during ERCP will confirm the diagnosis of pancreatic cancer.

**Angiography** Before the development of US, CT and ERCP, angiography was the only reliable imaging technique to diagnose pancreatic cancer. Currently angiography is used in some centers to assess resectability and for staging of pancreatic tumors (see below).

**Percutaneous fine-needle aspiration biopsy (FNA)**

Imaging studies of the pancreas can delineate structural abnormalities of the pancreas. Unfortunately, chronic pancreatitis can produce structural changes virtually identical to pancreatic cancer. Thus, in some cases cytologic or histologic confirmation of pancreatic cancer is necessary in order to plan medical or surgical therapy. FNA of the pancreas helps in the selection of patients suitable for surgery and to exclude those patients with unresectable tumors or with benign disease. FNA is usually performed under US or CT guidance. The sensitivity of FNA varies from 57% to 96%. However, FNA has a near perfect specificity with few false-positive results.[211,224-227] In about 10% of patients FNA

does not yield sufficient cellular material for diagnosis.[211] Furthermore, even after repeated sampling, a negative result cannot exclude the possibility that a malignant condition is present. It is possible that DNA analysis of specimens obtained with FNA may help in the diagnosis of pancreatic cancer. Tada et al [97] analyzed the DNA sequence around codon 12 of the K-ras oncogene in biopsy material and aspirates from patients with pancreatic cancer and pancreatitis. All specimens from 12 patients found to have pancreatic cancer had the mutation. No mutation was seen in 6 patients with chronic pancreatitis. This study is very exciting as it suggests that DNA analysis may improve our ability to diagnose pancreatic cancer with small amounts of tissue. Unfortunately, DNA analysis is still investigational and not widely available.

FNA is not without complications. Seeding of the needle tract with tumor,[228,229] and the possibility of increasing intraperitoneal spread [230,231] have been described.

The role of preoperative FNA for the diagnosis of pancreatic cancer is still controversial and most institutions do not perform FNA routinely.

**Endoscopic ultrasonography (EUS)**

In experienced centers, visualization of the head, body and tail of the pancreas can be achieved in the majority of cases.[232-234] EUS has been shown to be superior to US and CT in detecting pancreatic tumors, in particular small tumors (< 2cm).[234,235] Both the sensitivity and specificity of EUS for the diagnosis of pancreatic cancer are over 90%.[233-236] Tables 9 and 10 summarize the accuracy, sensitivity and specificity of EUS when compared to other imaging methods for the diagnosis of pancreatic cancer. The major problem with EUS is the inability of EUS to differentiate chronic pancreatitis from pancreatic tumors.

**Table 9**
**Reported accuracy of EUS compared to other imaging procedures in diagnosing pancreatic carcinoma in cases confirmed by histology**

| REFERENCE | n | EUS | US | CT | ERCP | ANGIO |
|---|---|---|---|---|---|---|
| Hayashi [233] | 30 | 97% | 87% | | | |
| Palazzo [236] | 49 | 96% | 65% | 69% | | |
| Yasuda [234] | 50 | 100% | 78% | 86% | 94% | 88% |
| Rosch [235] | 76 | 99% | 67% | 77% | 90% | |

Adapted from reference [232]

**Table 10**
**Sensitivity, specificity, and predictive value of EUS compared to other imaging procedures in the diagnosis of pancreatic tumors.**

| | EUS | US | CT | ERCP |
|---|---|---|---|---|
| Sensitivity | | | | |
| All tumors | 99% | 67% | 77% | 90% |
| Tumors < 3 cm | 100% | 50% | 55% | 90% |
| Specificity | 100% | 40% | 53% | 73% |
| Pos. predictive value | 100% | 79% | 85% | 92% |
| Neg. predictive value | 97% | 36%** | 50%** | 82% |

** ($p < 0.05$)
From reference [232]

**Staging**

The purpose of staging is to determine the extent of the disease in order to predict prognosis and to help in planning treatment. In the past, patients with suspected pancreatic cancer and no obvious metastasis were staged at the time of exploratory laparotomy. It was up to the surgeon to determine if the tumor was resectable or to treat the patient with palliative surgery. Currently, staging is used to determine patients presumed to have resectable tumors in whom curative surgery is attempted. Otherwise the role of surgery is limited to patients with duodenal obstruction.

The American Joint Committee on Cancer (AJC) staging classification uses the standard TNM format for staging pancreatic cancer (Table 11).[237]

**Table 11**
TNM criteria

| | |
|---|---|
| T1 | Tumor limited to the pancreas |
| T1a | Tumor < 2cm in greatest dimension |
| T1b | Tumor > 2cm in greatest dimension |
| T2 | Limited extension to duodenum, bile duct, peripancreatic tissue |
| T3 | Advanced local extension to major vessels stomach, colon, spleen |
| NX | Regional Lymph nodes can not be assessed |
| N0 | No nodal involvement |
| N1 | Involvement of regional lymph nodes |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

Group Staging Criteria

| | | | |
|---|---|---|---|
| Stage I | T 1-2 | N0 | M0 |
| Stage II | T 3 | N0 | M0 |
| Stage III | Any T | N1 | M0 |
| Stage IV | Any T | Any N | M1 |

The standard methods for preoperative staging have been CT and angiography. More recently, EUS and laparoscopy have enhanced our staging capabilities.

**CT** Is the most commonly used method to assess if the tumor is resectable. CT criteria that indicate that the tumor is not resectable include: a) invasion of peripancreatic fat, b) encasement of the superior mesenteric vein or artery, c) invasion of the duodenum or stomach, d) presence of regional lymph node enlargement, e) abnormal tissue in the porta hepatis and f) liver metastasis.[213] However, the absence of these criteria on CT does not guarantee resectability. In some cases, small pancreatic tumors that appeared resectable by CT proved to have local invasion and spread into regional lymph nodes at the time of surgery.[213] Furthermore, CT is not very sensitive for the detection of small liver and peritoneal metastasis.[238] In a recent study, CT was able to predict unresectable tumors in 100% of patients and resectable tumors in 72% of patients.[239]

**Angiography** With the use of US, CT and EUS for the diagnosis of pancreatic cancer, the role of angiography is limited to its ability to assess vascular involvement by the tumor.[240]

Although CT has been claimed to as good or better than angiography in evaluating vascular structures,[213,241] angiography and CT are probably complementary.[238] Another benefit of angiography is to give information about the vascular anatomy before surgery. In one study, 34% of patients evaluated for pancreatic cancer were found to have a major arterial anatomical anomaly.[242]

**ERCP** Has a limited role in staging. Tumor ingrowth into the duodenum as seen by ERCP indicates at least a T2 stage. The length of the stenosis in the bile or pancreatic ducts do not correlate with resectability.[243]

**EUS** can help in staging pancreatic tumors by determining tumor size and extent, regional lymph node and vascular involvement. The portal vein and its confluents, the mesenteric and splenic veins are the most important structures to investigate for tumoral vascular involvement.

The accuracy of EUS to determine the T and N stage of pancreatic tumors is over 90% and 70% respectively.[232,236,244-246] Although prognostically important, the presence or absence of enlarged lymph nodes is not crucial in determining resectability.[244,246] In two recent reports, EUS fared better than US and CT for local staging of pancreatic cancer (Table 12).

**Table 12**
**Accuracy of EUS compared to US and CT in local staging of pancreatic carcinoma**

| Reference | n | EUS | US | CT |
|---|---|---|---|---|
| T stage<br>Rosch | 35 | 94% | 37% | 49% |
| N stage<br>Rosch & Palazzo | 69 | 77% | 35% | 51% |

from reference [232]

Although angiography has been considered the gold standard for assessing vascular involvement, recent studies demonstrated that EUS was comparable or superior to angiography in determining involvement of venous structures (Table 13).[246-249]

**Table 13**
**Accuracy of EUS compared to other imaging techniques in the assessment of vascular invasion by pancreatic carcinoma**

| | n | EUS | US | CT | ANGIO |
|---|---|---|---|---|---|
| Sugiyama [248] | 5 | 100% | 60% | 20% | 100% |
| Snady [247] | 30 | 97% | | 53% | 80% |
| Rosch [246] ** | 40 | 95% | 55% | 73% | 85% |
| Pallazo [236] | 38 | 87% | 47% | 76% | |

** 12 patients with ampullary carcinoma are included in this study
Modified from reference [232]

However, angiography was more accurate in determining arterial involvement as the celiac axis is further away from the bowel lumen and therefore is more difficult to examine with EUS.[246,249]

In summary, EUS is very sensitive and specific for the diagnosis of pancreatic cancer. EUS is probably superior when compared to other imaging techniques for the diagnosis and staging of pancreatic cancer. However, EUS adds the risks inherent to endoscopic procedures (perforation, bleeding and infection), is unable to differentiate some cases of chronic pancreatitis from pancreatic cancer, and can overstage or understage tumors.

**Laparoscopy** The value of laparoscopy is its ability to detect small metastasis on the peritoneum or surface of the liver. Up to 40% of patients without evidence of metastasis on CT or angiography will prove to have small hepatic, omental or peritoneal metastasis.[238,250,251]

In a prospective study, patients with pancreatic cancer underwent CT, MRI, angiography and laparoscopy in the evaluation of resectability. The authors accurately determined the presence or absence of peritoneal or liver metastasis in 98% of patients. The authors concluded that CT, angiography and laparoscopy all made their own unique contribution to the diagnostic work-up before curative resection was attempted. However, MRI gave no extra information over contrast enhanced CT.[238]

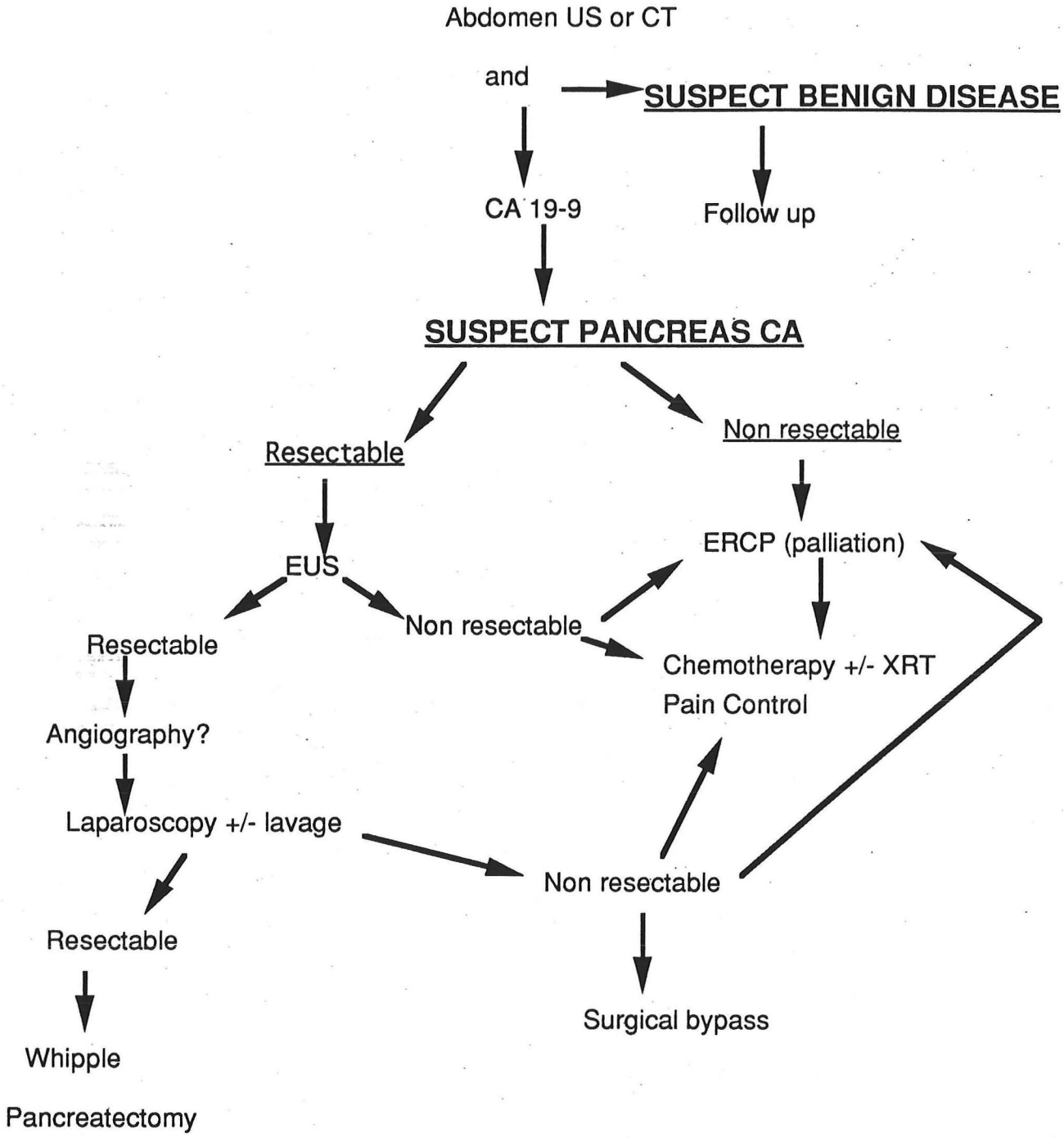
In an attempt to improve staging and assess resectability Warsaw et al examined the value of cytological examination of peritoneal washings obtained during laparoscopy or laparotomy. In 40 patients with pancreatic cancer, 12 (30%) were found to have malignant cells. It is of interest that a positive peritoneal lavage was present in 75% of patients who underwent previous percutaneous needle biopsy versus only 19% without previous biopsy. This raised the concern of spreading tumor with percutaneous needle biopsies. The presence of malignant cells on peritoneal lavage correlated with a shorter survival.[252]

**Diagnostic and staging strategy to determine treatment** (Table 14)

The initial evaluation of patients with suspected pancreatic cancer starts with CA 19-9 and CT. Patients with a normal CA 19-9 and CT who still have suspicious symptoms for pancreatic cancer should be reevaluated in 6-12 weeks. Patients with elevated CA 19-9 and evidence of tumor by CT should undergo staging to determine if the tumor is resectable. In patients with unresectable tumors, endoscopic drainage of the biliary tree, nutritional support and pain control should be carefully performed. Patients with tumors that appear to be resectable should undergo EUS and or angiography to further select patients with potentially curable tumors and obviate unnecessary surgery. If surgical resection is planned, the first operative step should be laparoscopy to rule out peritoneal and liver metastases. If no metastases are found the surgeon should proceed with resection of the tumor. If metastases are found or if the tumor is unresectable then surgical bypass of the biliary tree or gastrojejunostomy can be performed when considered necessary.

**Table 14**

# WORK UP FOR PANCREATIC CANCER



## Treatment

The four major therapeutic strategies include: a) surgery for cure, b) surgery for palliation with or without adjuvant therapy, c) management of advanced disease with chemotherapy, radiotherapy or a combination of both, and d) supportive care. Surgery offers the only hope for cure. Unfortunately, the diagnosis is usually made when the disease is already advanced and only a minority of patients have resectable tumor. Because therapeutic options leave much to be desired and are associated with significant toxicity and risks, many physicians have adopted a philosophy of therapeutic nihilism. However, different therapeutic options are available for palliation and in some patients can modestly improve survival.

### Curative surgery

Curative surgery is the only hope for cure in patients with pancreatic cancer. Unfortunately, only a small proportion of patients will be diagnosed early in the course of their disease with resectability rates around 15% (see Table 15).[253-256]

**Table 15**
**Resectability rates for pancreatic adenocarcinoma**

| Author | # patients | Patients resected | Resectability rate (%) |
|---|---|---|---|
| Morrow [254] | 225 | 39 | 17 |
| Nakase [256] | 2792 | 430 | 15 |
| Andren-Sandberg [255] | 641 | 91 | 14 |
| Connolly [253] | 766 | 89 | 12 |

Pancreaticoduodenectomy or the Whipple procedure is the surgery of choice for tumors located in the head of the pancreas. Distal pancreatectomy is used to treat tumors located in the body and tail of the pancreas. Unfortunately, most tumors in the body and tail of the pancreas are diagnosed late in their course and the prognosis is dismal despite surgical attempt for cure.[257]

Because pancreatic cancer can be multicentric in over 30% of cases,[258,259] some surgeons recommend total pancreatectomy regardless of the location of the tumor. Another theoretical advantage of total pancreatectomy is that it obviates the need of a pancreaticoenterostomy which is a common source of postoperative morbidity. However, total pancreatectomy has not proven to decrease surgical morbidity/mortality nor increase survival, and produces exocrine and endocrine pancreatic insufficiency.[255,258,260-262] Total pancreatectomy can be used as an alternative in patients in whom frozen sections of the proposed lines of resection are positive for cancer or if the condition of the remaining pancreas is not suitable for anastomosis.[260]

**Pancreaticoduodenectomy (Whipple procedure)** This formidable procedure involves resection of the head of the pancreas, proximal duodenum, gastric antrum, bile duct and/or gallbladder. Gastrointestinal continuity is reestablished with a choledochoenterostomy or cholecystoenterostomy, a gastrojejunostomy and a pancreaticojejunostomy.[263] This procedure preserves the distal pancreas which may prevent the development of diabetes or malabsorption due to pancreatic insufficiency. A modification of the Whipple procedure which preserves the pylorus and stomach has been used with similar results when compared to classical pancreaticoduodenectomy.[264-266] Patients that undergo the pylorus and gastric preserving procedure can eat normal sized meals and have a decreased risk of dumping symptoms.[264-266] In the period between 1960-1979 the Whipple procedure was associated with a 40-60% morbidity and a 20-40% mortality.[267,268] Over the past decade there has been a dramatic improvement in the outcome of patients undergoing pancreaticoduodenectomy with mortality rates under 5% (Table 16).[269-271] Even selected patients in their eight and ninth decades of life have a mortality rate of 5%.[272]

**Table 16**
**Morbidity and mortality rates after pancreaticoduodenectomy for pancreatic cancer**

| Author | Morbidity | Mortality |
|---|---|---|
| Crist [269] 1969-1980 | 59% | 24% |
| 1981-1986 | 36% | 2% |
| Trede [270] | 16% | 0% |
| Grace [271] 1975-1979 | 49% | 10% |
| 1980-1984 | 26% | 2% |
| Delcore [272] | 14% | 5% |

The most common cause of postoperative morbidity after pancreaticoduodenectomy is anastomotic leakage, in particular at the pancreaticoenteric anastomosis.[262,269,271,273] Other serious complications include hemorrhage, bilioenteric and/or gastroenteric fistulas and sepsis.[262,269,271,273]

The results of pancreaticoduodenectomy are far from satisfactory. As seen in Table 17, median survival and 5 year survival rates vary but are probably about 12 months and 10% respectively.

**Table 17**
**Median survival and 5 year survival rates after pancreaticoduodenectomy for pancreatic cancer**

| Author | Median survival (months) | 5 year survival (%) |
|---|---|---|
| Nakase [256] | 12 | 2 |
| Grace [271] | | 3 |
| Andren-Sandberg [255] | 11 | 5 |
| Crist [269] | | 18 |
| Cameron [265] | 12 | 19 |
| Trede [270] | | 36 |

Patients with small tumors, no vascular invasion and negative lymph nodes at the time of resection have a better survival.[265,269,270,274] Cameron et al reported that median survival in patients with negative lymph nodes at the time of surgery was 55.8 months compared to a survival of only 11 months in patients with lymph node involvement ($p < 0.5$).[265] Crist et al reported a 5 year survival of 48% in patients without lymph node involvement at the time of surgery and a 5 year survival of only 1% in patients with positive lymph node involvement (Figure 3).[269]

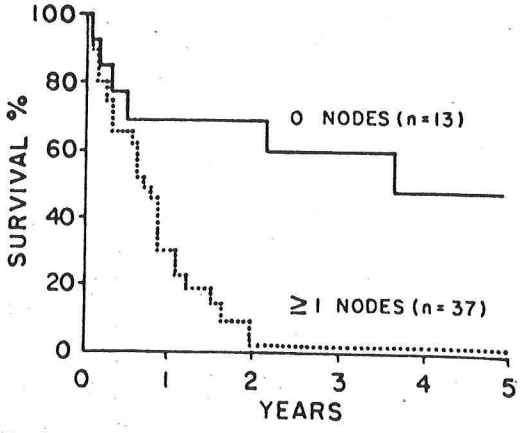



FIG. 2. Actuarial 5-year survival for those patients with adenocarcinoma of the pancreas with and without positive lymph node involvement.

## Palliation

**Biliary obstruction** Pancreatic cancer arises in the head of the organ in proximity to the intrapancreatic portion of the common bile duct and causes jaundice in 60-80% of cases.[47,79,82,83] In the past, surgery was the only way to palliate biliary obstruction. More recently, nonoperative methods (percutaneous and endoscopic) to decompress the biliary tree have been shown to have similar survival and lower complication rates when compared to surgery.[275-278] Furthermore, cost appears to be lower with endoscopic drainage when compared to surgery.[276]

In a randomized trial comparing endoscopic versus percutaneous drainage, the endoscopic method was more successful (81% versus 61%) and had a lower 30-day mortality (15% versus 33%) than the percutaneous method.[279] In experienced centers the success rate with the endoscopic method is about 90% and is associated with a

procedure-related mortality around 1-2%.[275,280,281] The disadvantages of the endoscopic method include the need for an experienced endoscopist, sophisticated fluoroscopy and endoscopic equipment, and a higher readmission rate due to stent occlusion and subsequent cholangitis. Stent occlusion can be prevented by using large caliber stents, prophylactic stent exchange in patients with prolonged survival, or using of metal stents that have a longer patency life when compared to polyethylene stents (273 versus 126 days).[282,283]

Surgical bilioenteric anastomosis was considered the gold standard therapy for palliation of obstructive jaundice. In a large review, mean in-hospital mortality was 18% and mean survival was 5.5 months.[284] Cholecystojejunostomy was thought to be the simplest, easiest and fastest technique for internal biliary decompression.[284] However, cholecystojejunostomy appears to have higher complication rates than choledochal-enteric anastomosis and in recent series this type of anastomosis is preferred over cholecystojejunostomy.[285,286]

Currently, endoscopic biliary decompression is the treatment of choice in patients who are not surgical candidates, leaving percutaneous drainage as an alternative for patients not suitable for endoscopic techniques. In patients who undergo laparotomy in an attempt for resection, biliary bypass can be performed and in most cases will prevent further need of therapy.

**Duodenal obstruction** is an unusual presentation occurring as a preterminal event in up to 15% of patients.[79,287] Carcinoma of the head of the pancreas tends to invade and obstruct the second portion of the duodenum while carcinoma of the body and tail invade the third and fourth portion of the duodenum. The only way to palliate duodenal obstruction is surgical gastrojejunostomy. Whether all patients all patients undergoing biliary bypass should undergo gastro-enteric bypass is a matter of debate. In a collective review of over 3,300 patients, about 16% of patients undergoing only palliative biliary diversion for unresectable pancreatic carcinoma required reoperation for duodenal obstruction.[284] Because the addition of a gastro-enteric bypass at the time of bilio-enteric bypass does not increase operative mortality,[284,288] some surgeons advocate prophylactic gastro-enteric bypass.[284,285] However, other studies have found increased morbidity after a double bypass,[286,289] and patients who require a gastrojejunostomy appear to have a dismal prognosis, making double bypass a futile effort.[286,290] Over the past 3 years there has been an explosion in the use of laparoscopy for surgical interventions and laparoscopic gastrojejunostomy may become the treatment of choice in patients with duodenal obstruction.[291]

**Single agent chemotherapy** Of many medications that have been tested as a single agent, only 5-FU has a response rate whose upper 95% confidence limit exceeds 20%.[47,292] The 5-FU response rate has been estimated to be 28%. However, this is probably an overestimate because this result was obtained from a compilation of studies with

response rates ranging from 0% to 67% and there were differences in patient selection and response criteria.[292,293] Ifosfamide was initially reported to have a high response.[294,295] However, further studies did not confirm this finding.[296,297] Epirubicin has been used as single agent or in combination with 5-FU or ifosfamide with poor results.[298] Cisplatin has also been used for the treatment of pancreatic carcinoma but has a modest activity.[299] Other drugs with reported activity include: mitomycin C, streptozotocin, adriamycin, melphalan and ibroplatin. A summary of the response rates of different drugs is shown in Table 18.

**Table 18**
**Response of pancreatic cancer to different chemotherapeutic agents**

| Drug | Number of responses/patients | Response Rate |
|---|---|---|
| 5-FU | 60/212 | 28% |
| Adriamycin | 2/15 | 13% |
| Melphalan | 2/15 | 13% |
| Ibroplatin | 3/30 | 10% |

Adapted from reference [293]

**Combination regimen chemotherapy** The most common regimens to treat pancreatic cancer are: FAM (5-FU, adriamycin and mitomycin-C) and SMF (streptozotocin, mitomycin-C and 5-FU). In some studies the response rates for FAM range from 13% to 37%,[300-302] and response rates for SMF range from 15% to 43%.[303-305] However, results of other randomized studies have had much lower response rates. One randomized trial comparing FAM and SMF in 184 patients yielded only a 14% and 4% response rate, with a median overall survival of 26 and 18 weeks, respectively.[306] Another randomized study using 133 patients compared FAM and two different SMF regimens and found response rates of 13-15%.[301] The response rate of a phase III study using FAM and SMF was also very disappointing.[307] Other phase II studies using different chemotherapy combinations have failed to improve survival significantly in patients with pancreatic carcinoma.[308-310]

In summary, there is no chemotherapeutic regimen in the treatment of advanced pancreatic carcinoma that has good response rates or improves survival significantly. Patients treated with chemotherapy should be enrolled in controlled trials.

**Radiation therapy (XRT)**
Radiation therapy can palliate pain in over 50% of patients with unresectable pancreatic cancer.[311-313] Unfortunately, radiotherapy alone does not seem to significantly improve survival.[314,315] The combination of radiotherapy and chemotherapy (5-FU) appears to be superior to radiotherapy alone for palliation of unresectable pancreatic cancer.[315]

Radiotherapy in combination with chemotherapy also seems to improve survival. In a prospective trial, radiotherapy (4,000 Rads) plus chemotherapy (5-FU) was compared to no adjuvant therapy in 43 patients with unresectable pancreatic cancer. The median survival was 20 months for the treatment group and 11 months for the control group.[316] A subsequent study with a similar protocol also had encouraging results and the authors recommended adjuvant therapy over no therapy.[317] Radiotherapy in combination with chemotherapy is also superior to chemotherapy alone. In a prospective randomized trial, chemotherapy alone (SMF) was compared to radiation therapy plus 5-FU. Survival of patients treated with the combination radiotherapy plus chemotherapy arm was significantly longer than patients treated with chemotherapy alone.[318] Other agents such as adriamycin, cisplatin and mitomycin in combination with radiotherapy have been used.[319] It is controversial at this point if these agents significantly improve survival compared to the use of radiotherapy and 5-FU alone. In some cases a high grade of toxicity has been observed.[318,320]

**Intraoperative radiation therapy (IOEBT)** Using IOEBT very high doses of radiation can be delivered to carefully restricted areas of tumor, avoiding irradiation of surrounding normal tissue.[321] IOEBT seems to be very effective for relieving pain in 50% to 93% of patients.[322-324] However, it is unclear if IOEBT improves survival.[325,326] In a review of 720 patients with unresectable pancreatic carcinoma treated with IOEBT, the median survival ranged from 5.8 to 13.5 months.[324] A recent study combining IOEBT and intraoperative interstitial microwave hyperthermia suggested an improved survival in patients with unresectable pancreatic cancer.[327] However, a controlled randomized trial should be done to confirm this preliminary observation. IOEBT can be associated with severe complications, including gastrointestinal bleeding, obstruction, perforation in up to 30% of patients, retroperitoneal fibrosis and pancreatic insufficiency.[321,324,328] In summary, IOEBT has not proven to be more effective than conventional external beam radiation and controlled randomized studies should be done to determine its role in the treatment of unresectable pancreatic cancer.

**Implantation of radioactive agents** The goal of implanting radioactive agents is to deliver high radiation dose to the tumor without damaging neighboring organs. The most common technique is intraoperative implantation of $^{125}$Iodine followed by external beam radiotherapy and or chemotherapy. A recent non randomized study suggested that selected patients with unresectable pancreatic cancer, treated with a combined regimen of intraoperative

implantation of $^{125}I$, external beam radiation, and perioperative chemotherapy appear to have better palliation and survival than that reported with other therapeutic approaches.[329] However, several other studies have not shown any significant improvement in survival or palliation.[324,330,331] Serious complications such as pancreatic fistulization and gastrointestinal bleeding have been described.[324,331] Recently percutaneous, ultrasonically guided implantation of $^{125}I$ has been described.[332] This technique avoids surgical risks and is associated with mild discomfort. However, survival time and palliation is poor and this technique can not be recommended as standard therapy.

**Other therapies** Because pancreatic cancer is considered to respond poorly to radiotherapy and chemotherapy, other non conventional therapies such as hormones, monoclonal antibodies, and interferon have been tried.

**LH-RH analogues** The identification of sex hormone receptors in human pancreatic cancer fueled hopes for a new therapeutic strategy, similar to hormonal manipulation in breast and prostate cancers. LH-RH analogues inhibit the pituitary-gonadal axis creating a state of sex hormone deprivation. In theory, this may inhibit pancreatic cancer growth. Although initial studies using LH-RH analogues were encouraging,[333,334] more recent studies have failed to show tumor response or improvement in performance status with LH-RH analogues.[335-337]

**Tamoxifen** The effect of tamoxifen in the treatment of pancreatic cancer is also controversial. While some studies demonstrated an improved survival in patients with advanced pancreatic cancer treated with tamoxifen.[338] Other studies found no beneficial effect of tamoxifen.[339] In a recent randomized placebo-controlled trial tamoxifen did not improve survival in 44 patients with unresectable pancreatic cancer.[340]

**Somatostatin** appears to inhibit pancreatic cancer growth in animal models.[135-137] In humans, 19 patients with advanced pancreatic cancer were treated with a somatostatin analogue (BIM 23014). Six patients had a reduction in pain and improvement in performance status (32%). However, tumor growth was retarded in only one patient.[341]

**Cholecystokinin (CCK)** As mentioned above, CCK appears to stimulate the growth of pancreatic neoplasms in animal models [120,121] and in pancreatic cancer cell lines.[119,127,128] In addition, the use of CCK antagonists may inhibit the growth of pancreatic cancer.[123,124] In a recent human study, a CCK receptor antagonist (MK-329) failed to demonstrate any impact in tumor progression, pain control, or nutrition in 18 patients with advanced pancreatic cancer.[342]

**Alpha interferon** Recombinant α-interferon seems to have a synergistic effect with 5-FU in the treatment of metastatic gastrointestinal malignancies.[343] However, uncontrolled trials using the combination of α-interferon and 5-FU in the treatment of advanced pancreatic adenocarcinoma have failed to improve survival,[344-346] and can be associated with severe toxicity (stomatitis, diarrhea and granulocytopenia).[344,346]

**Tumor necrosis factor (TNF)** Recombinant TNF appears to have some activity against gastrointestinal tumors.[347] However, TNF does not seem to be effective for the treatment of pancreatic carcinoma.[348]

**Immunotherapy with monoclonal antibodies** The rationale of using monoclonal antibodies to treat cancer is based on their direct antitumor effect and/or the induction of human anti-idiotype response which is like a vaccination against the tumor.[349-351] Initially, uncontrolled studies found that monoclonal antibodies could produce pancreatic cancer regression in up to 21% of patients with little toxicity.[352,353] Unfortunately, a recent controlled trial failed to demonstrate any improvement in survival or tumor regression in 61 patients with advanced pancreatic adenocarcinoma treated with monoclonal antibodies.[354]

**Lovastatin** (Mevacor), inhibits the growth of different human and animal pancreatic cancer cell lines tested in vitro and in nude mice.[355] The inhibitory effect of Lovastatin can be completely prevented by concomitant addition of mevalonic acid.[355] A possible mechanism for this growth-inhibitory effect of Lovastatin is suggested by recent studies showing that the Ras protein is normally bound to the cell membrane with an intermediate product of cholesterol biosynthesis (farnesyl isoprenoid) [356] and seems to be essential for Ras function.[357,358] Lovastatin a 3-Hydroxy-3-methylglutaryl coenzyme A antagonist inhibits the conversion of HMG-CoA to mevalonic acid, and in turn, the subsequent production of isoprenoid metabolites.

**Pancreatic cancer and toxins** In vitro, both cholera and clostridium difficile toxins inhibit the growth of human pancreatic cancer cell lines.[359,360] The clinical significance of these experimental findings is yet to be defined.

**Pain control** Pain is present in the majority of patients with advanced pancreatic cancer and is often the dominant symptom. Most patients do not respond to non-narcotic analgesics, and require narcotic analgesics. It is common to combine a nonsteroidal and narcotic analgesics. If pain control is inadequate with oral analgesics, subcutaneous or epidural administration of narcotic analgesics can be done using a dose-pump.[361] As mentioned above, radiotherapy seems to relieve pain in a significant proportion of patients and should be considered.[311-313]

Celiac plexus blockade with alcohol is another alternative for patients with untractable pain. Celiac plexus blockade can provide pain relief in the majority of patients and may last until death.[362-365] Celiac blockade is usually performed by an anesthesiologist under fluoroscopic or CT guidance.[362,363,366] Complications include orthostatic hypotension, dizziness, increased gut motility, urinary retention, impotence, neurologic symptoms and paraplegia.[362-364,366]

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