Pancreatic Cancer

*Steven J. Cohen, MD**
Wayne H. Pinover, DO[†]
James C. Watson, MD[‡]
*Neal J. Meropol, MD**

Address
Departments of Medical Oncology*,
Radiation Oncology[†], and Surgical Oncology[‡],
Fox Chase Cancer Center, 7701 Burholme Avenue,
Philadelphia, PA 19111, USA.

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Opinion statement

Optimal therapy for pancreatic adenocarcinoma requires surgical removal with tumor-free margins. Superior outcomes have been reported for high-volume centers incorporating a multidisciplinary approach. Postoperative ("adjuvant") chemotherapy and radiation should be considered in patients with successfully resected primary tumors. Combined modality treatment with chemotherapy and radiation should be considered for locally advanced, unresectable tumors. Gemcitabine can provide symptom relief and a modest improvement in survival for patients with metastatic disease. Strict attention to relief of symptoms such as pain, depression, anorexia/cachexia, and jaundice is essential in all patients with pancreatic cancer. All patients with pancreatic cancer should be encouraged to enter clinical trials of new therapies, given that long-term survival for all stages remains poor.

Introduction

Cancer of the exocrine pancreas is one of the most devastating of human cancers. It is the fifth leading cause of cancer death in the United States, with an estimated 28,300 new cases in 2000, and an almost equal number of deaths expected [1]. The disease is slightly more prevalent in women. Incidence increases with age, and most patients are diagnosed after age 50 years. The overall outlook for the disease remains dismal; 5-year survival rates are approximately 5% to 20% for those with resectable disease. Among those whose disease is unresectable, median survival for metastatic and locally advanced disease averages 5 and 10 months, respectively.

The most consistently identified risk factor for pancreatic cancer is cigarette smoking. Other risk factors include chronic pancreatitis (acquired or hereditary) and diabetes. Rare genetic syndromes associated with pancreatic cancer include hereditary pancreatitis, the familial pancreatic cancer syndrome, hereditary nonpolyposis colon cancer, familial atypical mole melanoma, familial adenomatous polyposis, Li-Fraumeni syndrome, and Peutz-Jeghers syndrome [2]. Somatic gene mutations associated with pancreatic cancer are also being defined. Mutations in tumor suppressor genes, such as p53, p16 (MTS1), or DPC4, or inappropriate activation of oncogenes such as K-*ras*, are commonly present in sporadic pancreatic cancers. Mutations in p16 were found in nearly 80% of specimens from patients with sporadic pancreatic adenocarcinoma in one series [3] and are mutated in the germline in some families with familial pancreatic cancer [4]. DPC4 was found to be inactivated in nearly 50% of pancreatic cancers [5], and p53 mutations occur in approximately 75% [6••]. Somatic mutations of K-*ras* are nearly universal and are therefore the most common genetic abnormality in pancreatic cancer. Germline mutations of the *BRCA2* gene predispose carriers to an increased risk of pancreatic cancer, with mutations discovered in 7% of apparently sporadic pancreatic cancers in one series [7]. Recently, a progression model for pancreatic cancer has been described [8••].

In patients with signs and symptoms of pancreatic cancer, an appropriate diagnostic and staging workup is essential (Fig. 1). Symptoms suggestive of pancreatic

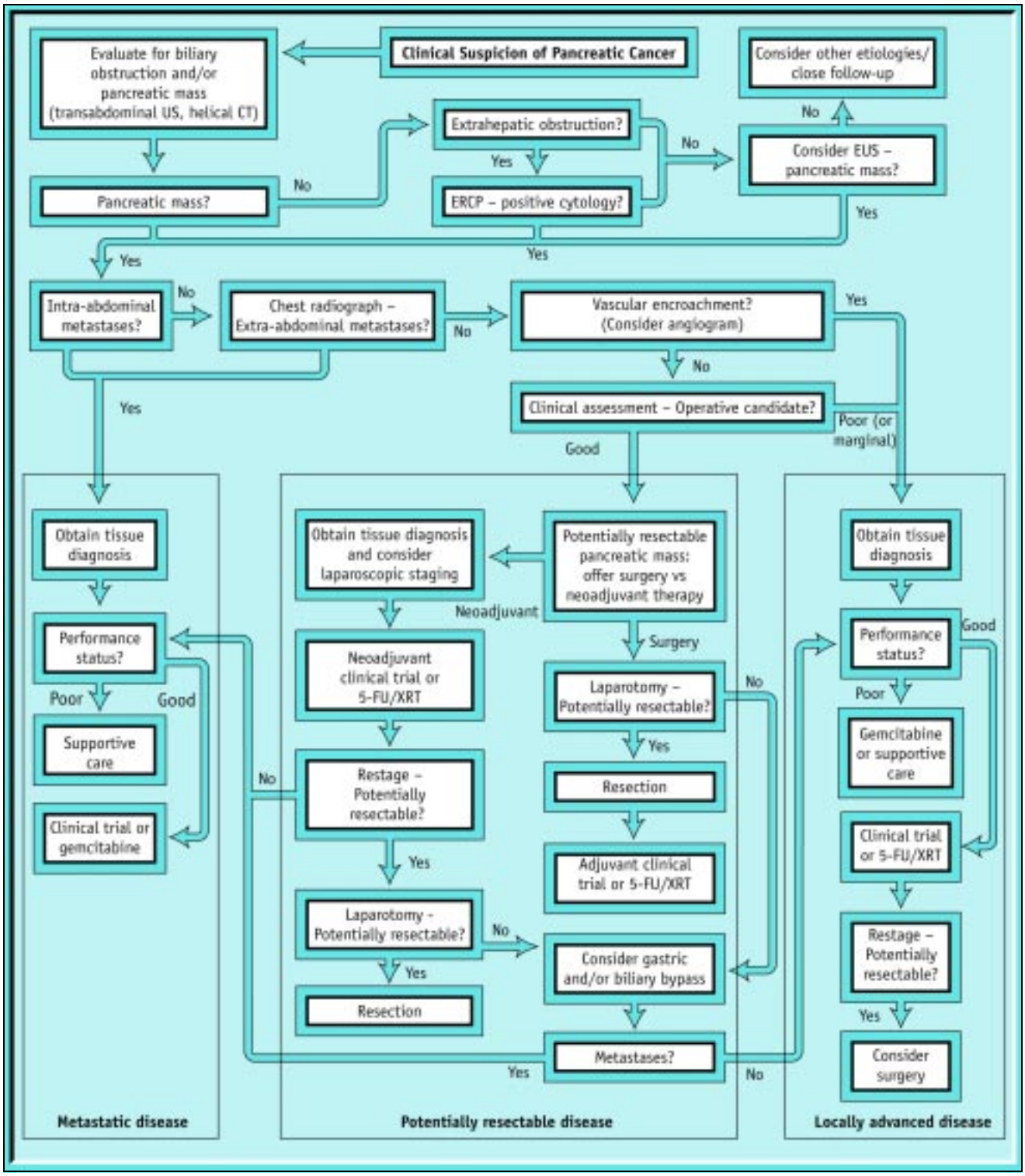

Figure 1. Algorithm outlining the approach to diagnosis, staging, and treatment of pancreatic cancer.
CT—computer tomography; ERCP—endoscopic retrograde cholangiopancreatography; EUS—endoscopic ultrasound; 5–FU/ XRT—5–fluorouracil/external beam radiotherapy.

cancer include painless jaundice, abdominal or back pain, nausea and vomiting, and weight loss. In patients with jaundice, a transabdominal ultrasound is often the first diagnostic test obtained. Although it can aid in identifying the level of biliary obstruction and distinguish between intra- and extrahepatic causes of jaundice, its role in staging is limited. Computed tomography (CT) in the form of helical or spiral imaging has greater accuracy than transabdominal ultrasound in diagnosing and staging pancreatic tumors [9].

Table 1. Diagnostic and staging modalities for pancreatic cancer

Chest radiograph
Endoscopic retrograde cholangiopancreatography
Endoscopic ultrasound
Helical computed tomography scan
Laparoscopy
Percutaneous transhepatic cholangiography
Transabdominal ultrasound
Visceral arteriogram

Helical CT may accurately predict resectability in most cases [10]. An emerging staging modality is endoscopic ultrasound, which is more accurate than CT scan in the evaluation of small (< 3 cm) lesions to determine vascular invasion [11,12]. Other tests useful in diagnosis and staging include the CA 19-9 blood test and a chest radiograph. One prospective study found that in nonjaundiced patients, CA 19-9 above 100 U/mL greatly increased the positive predictive value of imaging modalities for diagnosing pancreatic cancer [13]. In patients with jaundice and a classic presentation, the CA 19-9 added little information. A chest radiograph should be obtained in patients with suspected or diagnosed pancreatic cancer to rule out lung metastases. Table 1 lists available diagnostic and staging studies for pancreatic cancer.

Determination of diagnosis preoperatively by fine-needle aspiration is not required when a patient presents with a typical history and pancreatic mass. Certain situations in which histologic diagnosis is essential include consideration of neoadjuvant treatment or in patients in whom the primary treatment modality will not include surgery (locally advanced or metastatic disease). In these circumstances, a tissue diagnosis must be obtained because benign conditions (*eg*, chronic pancreatitis) can masquerade as malignancy. Finally, it is important that any patient being considered for curative surgery undergo an adequate nutritional assessment. In patients in whom jaundice or local symptoms preclude adequate preoperative oral intake, total parenteral nutrition may be used.

The staging system for pancreas cancer follows the American Joint Committee on Cancer Staging tumor, nodes, and metastasis classification [14]. Stages I and II include cancers that do not involve regional lymph nodes. Stage I incorporates tumors confined to the pancreas, tumors that are smaller than 2 cm (T1), or tumors that are larger than 2 cm (T2). Stage II refers to tumors directly invading the duodenum, bile duct, or peripancreatic tissues (T3). Stage III represents regional lymph node involvement. Tumors with direct extension to other organs or distant spread are classified as stage IV. Unfortunately, only 5% to 20% of patients are found to have localized, resectable disease after clinical staging procedures described above. The remainder have locally advanced or metastatic disease.

The remainder of this article focuses on treatment options for pancreatic cancer. Discussion is limited to adenocarcinoma of the ductal epithelium of the exocrine pancreas because this disease comprises 90% of pancreatic malignancies. First, the treatment approach for those patients with clinically resectable disease is considered. Subsequently, adjuvant and neoadjuvant chemoradiation strategies for resectable patients are discussed. Chemotherapy or combined chemoradiation treatment plans are reviewed for the vast majority of patients with unresectable disease. Symptomatic management and emerging and future treatment options are also considered.

Treatment

Endoscopy

- Endoscopic procedures have a role in the diagnosis, staging, and palliative therapy of pancreatic cancer. Endoscopic retrograde cholangiopancreatography (ERCP) is useful for diagnosing pancreatic tumors when there are suggestive signs and symptoms but no obvious pancreatic mass detected by other studies, and for placing biliary stents.
- The routine use of preoperative biliary drainage cannot be recommended except in instances where biliary obstruction is longstanding (serum bilirubin exceeds 15 mg/mL), or when surgery will be delayed due to patient malnourishment or neoadjuvant therapy.
- Endoscopic ultrasound (EUS) can accurately locate and locally stage pancreatic cancer and enable fine-needle aspiration biopsy. It is more accurate than CT scan for staging smaller pancreatic malignancies as well as detecting vascular invasion and local resectability [12].

Endoscopic retrograde cholangiopancreatography

Standard procedure	Endoscopic retrograde cholangiopancreatography should demonstrate both bile and pancreatic ducts in more than 80% of cases. Failure to achieve a diagnosis can result either from failure of cannulation or from cannulation of a nondiagnostic duct. Complete pancreatic duct obstruction is almost always diagnostic of malignancy. Routine collection of pancreatic juice for cytologic analysis (30% to 80% accuracy) should be performed.
Contraindications	Prior gastric resection with Bilroth II anastomosis, retained visceral barium, acute pancreatitis, acute cholangitis.
Complications	Cholangitis or pancreatitis may occur with unrelieved ductal (usually biliary) obstruction that is contaminated or aggravated by retrograde injection of contrast material. An increase in postoperative infectious complications and death may occur if unnecessary preoperative biliary drainage is performed [15]. However, in patients in whom neoadjuvant chemoradiation is planned, a recent review suggests that stent-related complications following therapy are relatively infrequent [16].
Special points	Endoscopic retrograde cholangiopancreatography is generally unnecessary in a patient with a typical clinical history and pancreatic mass on CT.

Endoscopic ultrasound

Standard procedure	Endoscopic ultrasound through the stomach or duodenum can detect small lesions in the pancreas and their relation to portal vasculature, biliary and pancreatic ducts, and surrounding lymph nodes. If needed, fine-needle aspiration can be performed.
Contraindications	Inability to tolerate endoscopy, prior determination of unresectable disease.
Complications	Perforation, bleeding.
Special points	Role in work-up still emerging. Results are highly dependent on operator experience.
Cost effectiveness	May decrease the need for additional invasive tests if unresectability demonstrated.

Percutaneous transhepatic cholangiography

- Initially introduced as a diagnostic procedure, percutaneous transhepatic cholangiography (PTC) has been extended to provide internal drainage in patients with obstructive jaundice due to an unresectable pancreatic cancer. It enables successful drainage in nearly 95% of patients [17].

Percutaneous transhepatic cholangiography

Standard procedure	Diagnostic cholangiography is performed to define site of bile duct obstruction and to note biliary drainage pattern. Internal-external drainage catheter placement follows. After initial external biliary drainage, an internal endoprostheses may be placed (if possible) for long-term drainage. In patients with complete duct obstruction, often only external drainage is possible.
Contraindications	Coagulation abnormalities, stents unnecessary if curative surgery is immediately planned.
Complications	Sepsis/cholangitis, fever, subcapsular hematoma, and bleeding occur infrequently (10% of cases) and generally only transiently. Symptoms of sepsis/cholangitis should be treated by rapid radiologic catheter evaluation, manipulation, or replacement.
Special points	Patients with external drainage catheters should be instructed on appropriate sterile catheter flushing.

Staging laparoscopy

- Despite optimal preoperative radiologic staging (Table 1), many patients with pancreatic cancer are found at exploration to be unresectable due to the presence of peritoneal implants, liver metastases, or extensive vascular involvement [18]. Diagnostic laparoscopy can reduce the number of unnecessary open explorations in this patient population [18].
- When compared wih laparotomy without resection, laparoscopy significantly shortens the length of hospital stay [19].
- Laparoscopy may be used in patients considering neoadjuvant therapy to identify those with subclinical metastases for whom later resection may not improve outcome.

Diagnostic laparoscopy

Standard procedure	A thorough exploration of the abdominal cavity is essential in ruling out metastatic disease to the liver surface/parenchyma, peritoneum, and pelvis.
Contraindications	Comorbid disease precluding operation, inability to safely access peritoneum for CO_2 insufflation, adhesions limiting thorough laparoscopic exploration.
Complications	Minimal. Unknown rate of port-site recurrence (port sites are often excised at time of resection).
Special points	Peritoneal wash may be performed at time of laparoscopy to evaluate for shedding of malignant cells. Positive peritoneal cytology is associated with advanced disease and is highly specific for predicting unresectability of pancreatic cancer [20].
Cost effectiveness	Decreased hospital stay in patients found to have unresectable disease and thus spared laparotomy.

Surgery

- Surgery with curative intent should be undertaken only when preoperative staging (Table 1) indicates resectability. Surgery can also be undertaken for palliation of symptoms related to obstruction or bleeding.
- Major pancreatic surgeries performed at high-volume centers are associated with significantly reduced operative mortality rates compared with low-volume centers (less than 6% compared with 12.9%, respectively) [21–23].
- Tumor extension to the margins is common in surgery for pancreatic cancer and is a strong predictor of treatment failure. Patients undergoing pancreaticoduodenectomy for cancer of the head of the pancreas with both negative lymph nodes and negative margins have a median survival of 32 months and a 5-year survival of 40% [24]. In contrast, patients resected with positive margins have a median survival of 10 months and a 5-year survival of 8% [25].

Pancreaticoduodenectomy (Whipple operation)

	The Whipple operation, although having undergone numerous modifications and technical refinements since its introduction in the mid-1930s, remains the extirpative surgical procedure of choice for pancreatic adenocarcinoma. Its three phases include determination of resectability, resection, and reconstruction.
Standard procedure	Determination of resectability: Must be initially performed in all patients without committing to an extensive pancreatic or gastrointestinal operation in order to confirm resectability. Rule out implants on peritoneal surfaces (lining solid organs, viscera, and pelvis), tumor nodules within the liver, or involvement of perihepatic lymph nodes (outside the field of resection). Rule out extensive tumor involvement of the superior mesenteric artery (SMA), hepatic artery, or portomesenteric veins.

Involvement of the SMA makes the patient unresectable for cure. However, in certain cases it may be possible to resect and reconstruct portions of either the hepatic artery or the portomesenteric veins to obtain negative surgical margins.

Resection: Meticulous attention during all dissection phases should be used to ensure adequate negative margins and avoid excess blood loss. Perform cholecystectomy and divide the stomach (or duodenum, for a pylorus-sparing pancreaticoduodenectomy), common bile duct and proximal jejunum. Ligate/divide the gastroduodenal artery and collateral vessels between portomesenteric vessels and pancreas. Divide pancreas (typically using electrocautery) and remove specimen (for standard pancreaticoduodenectomy this includes gastric antrum, duodenum, common bile duct, pancreatic head with uncinate process, portion of proximal jejunum, and peripancreatic tissue containing lymph nodes). Obtain frozen section of the transected pancreas to ensure that microscopic tumor does not extend to the line of resection. Biopsy firm areas in the pancreas distal to the resection; if suspicious for cancer additional pancreas should be resected, or a total pancreatectomy should be performed. Vascular resection and reconstruction should be used when portomesenteric encroachment exists.

Reconstruction: The order of reconstruction of gastrointestinal continuity and the routine use of stents at the pancreaticojejunostomy and hepaticojejunostomy is one of personal preference. Usually the pancreatic or bile duct anastomosis is accomplished first. Because fear of anastomotic leak at the pancreaticojejunostomy is genuine, it is preferable to suture the pancreatic duct mucosa precisely to the jejunal mucosa. Construct hepaticojejunostomy distal to the pancreaticojejunal anastomosis. Technical factors determine the site of this anastomosis. Complete gastrointestinal continuity with the formation of a gastrojejunostomy (or duodenojejunostomy, for a pylorus-sparing pancreaticoduodenectomy). Although not essential, creation of a Braun side-to-side jejunojejunostomy allows bile and pancreatic secretions to bypass the stomach and may help prevent bile gastritis. Place drains in the area of the pancreaticojejunostomy and choledochojejunostomy to detect and drain potential leaks after surgery.

Portomesenteric vascular resection and reconstruction: Inability to separate the pancreas from the portal vein has historically been a locoregional contraindication to resection in patients harboring a pancreatic cancer. However, abutment or encasement by tumor in the "field of resection" does not necessarily indicate unresectability in all cases [25]. Isolated portomesenteric vein involvement can be resected and reconstructed (using analogous saphenous or femoral vein) safely with a low perioperative mortality rate [26]. Patients requiring portal vein resection (PVR) have an overall survival (13 months) that is not significantly different from those without PVR [25]. Pathologic review of resected portomesenteric veins demonstrates tumor invasion into the vein wall in 71% of cases [26].

Contraindications Comorbid conditions precluding surgery, distant metastases, or unresectable disease.

Complications Early delayed gastric emptying (19%), pancreatic fistula (14%), wound infection (10%) [27•].

Special points Perioperative blood transfusion has been reported to be associated with decreased survival [28], but this may reflect the necessity of more complex surgery in these patients due to locally advanced disease.

Total pancreatectomy

Total pancreatectomy (TP) was initially introduced to deal with foci of cancer potentially remaining in the unresected pancreas and to avoid fistula formation from the pancreaticojejunal anastomosis. It has equivalent morbidity and long-term survival compared with a Whipple procedure, and most surgeons reserve it for extensive or diffuse pancreatic cancers.

Standard procedure Essentially a pancreaticoduodenectomy with the addition of a distal pancreatectomy with or without splenectomy.

Contraindications Similar to pancreaticoduodenectomy.

Complications Diabetes.

Special points Greater number of lymph nodes removed compared with pancreaticoduodenectomy, but without change in prognosis.

Palliative gastrojejunostomy and biliary bypass

	For patients taken to laparotomy but found to be unresectable, operative palliation is a worthwhile goal. Patients with greater than 6 months life expectancy may benefit from surgical biliary bypass because percutaneous or endoscopically-placed stents are prone to occlusion [29].
Standard procedure	Open or laparoscopic gastrojejunostomy and cholecystojejunostomy can be performed to relieve or prevent enteric obstruction and to relieve and correct jaundice.
Contraindications	Comorbid condition precluding operation. Adhesions may preclude CO_2 insufflation and limit ability to perform laparoscopy.
Complications	Postoperative respiratory complications, gastrointestinal bleeding, wound infection, or cholangitis are experienced by 20% to 60% of patients [30].
Special points	The need for therapeutic double bypass is a bad prognostic factor. An added prophylactic bypass increases morbidity without impacting survival; most patients die from their disease before obstructing or hemorrhaging [31].

Adjuvant therapy

- Despite improved surgical technique, the 5-year survival of patients undergoing pancreaticoduodenectomy with curative intent is no better than 20%, even at high-volume centers [24]. Because failure is common both locally and distantly [32], postoperative chemotherapy and radiation has been investigated to eradicate any residual microscopic disease.
- Support for a benefit from postoperative chemotherapy plus radiation therapy came from a small study of the Gastrointestinal Tumor Study Group (GITSG). A prospective, randomized trial compared postoperative chemoradiation (see acceptable regimens, below) to observation in patients who had undergone curative resection for ductal, acinar, or undifferentiated adenocarcinoma of the pancreas. The treatment group showed benefit in both median (20 vs 11 months) and 2-year survival (43% vs 18%) (32). This study has been criticized because of its small sample size (n = 43), prolonged recruitment of patients over 8 years, and early termination prior to reaching original recruitment goal.
- A recently reported study by the European Organization for Research and Treatment of Cancer (EORTC) readdressed the issue of adjuvant therapy, randomizing patients with cancers of both the head of the pancreas and the periampullary region to postoperative chemoradiation or observation. The radiation schedule was similar to the GITSG study. 5-fluoruoracil (5-FU) was given as a continuous infusion rather than bolus for the first week of each 2-week radiation course and not continued after radiation, in contrast to the GITSG regimen. In the patients with pancreatic cancer, the treatment group showed a trend (P = 0.099) toward improvement in median (17 vs 12 months) and 5-year survival (20% vs 10%) [34]. However, 21 of 104 patients randomized to receive adjuvant therapy never received it. Given the intent-to-treat nature of the analysis, this may have decreased the chances of finding a statistically significant survival advantage in favor of treatment.
- Given the positive GITSG trial and the trend observed in the EORTC study, postoperative chemoradiation should be considered in patients not eligible for a clinical trial. Given theoretic evidence of decreased effectiveness of split course radiation, plus clinical evidence of tolerability of continuous schedules, we prefer the latter approach. Likewise, continuous infusion 5-FU is tolerable and may provide improved radiosensitization compared with bolus dosing [35]. The contribution of 5-FU following combined therapy is uncertain given its minimal activity against advanced pancreatic cancer [36•].
- The use of gemcitabine in the adjuvant setting is not established.

Adjuvant chemoradiation

Acceptable regimens	**GITSG regimen:** Split course radiation therapy delivered in two courses of 20 Gy (2 Gy fractions, 5 d/wk) for a total of 40 Gy. Each course is separated by 2 weeks. 5-FU given by intravenous bolus at 500 mg/m² on the first 3 days of each radiation course, then once weekly for 2 years or until tumor progression. **Preferred by authors:** Radiation therapy delivered in 1.8 Gy fractions to a total of 45 to 50 Gy over 5 to 6 weeks without break. 5-FU is given as continuous infusion during radiation at a dose of 225 mg/m^2/d (7 d/wk) or 300 mg/m^2/d (5 d/wk). **Control arm of current North American Intergroup trial**: 3 weeks of continuous infusion (CI) 5-FU at 250 mg/m^2/d (1–2-week break). Radiation therapy delivered in 1.8 Gy fractions to 50.4 Gy over 5.5 weeks with CI 5-FU, 250 mg/m^2/d during radiation (3- to 5-week break). 2 cycles of CI 5-FU (one cycle = 4 weeks of CI 5-FU at 250 mg/m^2/d followed by 2-week break).
Contraindications	Prior radiation therapy, inflammatory bowel disease, scleroderma, systemic lupus erythematosus, significant renal insufficiency, poor nutritional or performance status postoperatively, discovery of metastatic disease.
Main drug interactions	With 5-FU: Allopurinol, methotrexate, leucovorin, interferon-α, interferon gamma, hydroxyurea.
Main side effects	Abdominal discomfort, nausea, mucositis, diarrhea, anorexia, weight loss, myelosuppression, cardiac ischemia, cerebellar ataxia, neurologic dysfunction, hand-foot syndrome, conjunctivitis, rash.
Complications	Dose-limiting organ toxicity with radiation includes effects upon the small intestine, stomach, liver, kidneys, and spinal cord. Incidence of severe gastrointestinal complication (ulceration or obstruction) is less than 10% at radiation doses less than 55 Gy. Less than 5% risk of late fulminant hepatitis, veno-occlusive disease, biliary duct stenosis.
Special points	Patients with normal renal function must not receive more than 20 Gy to greater than 50% of the total functioning renal parenchyma. Use of CT simulation and conformal treatment may improve tolerability of radiation therapy. Adjuvant therapy should preferably begin within 6 weeks of surgery.

Neoadjuvant therapy

- Preoperative chemoradiation allows for delivery of radiation and chemotherapy to a tumor with an undisturbed vascular supply. It may also improve resectability and decrease tumor dissemination at the time of surgery.
- Neoadjuvant therapy can prevent unnecessary surgery in patients who develop preoperative metastatic disease. It avoids treatment delays or discontinuation resulting from prolonged postoperative recovery.
- Hoffman *et al.* [37] demonstrated the feasibility of preoperative chemoradiation in the cooperative group setting, combining 50.4 Gy of external beam radiation with 5-FU–based chemotherapy in 53 patients. All were considered resectable on the basis of preoperative staging studies. Forty-five percent of patients were ultimately found to be resectable, with a median survival of 15 months for those undergoing curative resection.
- Neoadjuvant therapy is not standard of care at this point; it is not clear how resection rates or survival compare with surgery alone or with surgery followed by adjuvant therapy. Randomized comparisons between neoadjuvant and adjuvant therapies are required, and current clinical trials are ongoing to evaluate newer chemotherapy agents such as gemcitabine with radiation for preoperative and postoperative therapy.

Therapy for locally advanced disease

- For patients with locally advanced, unresectable disease and adequate performance status, combined modality therapy with chemoradiation should be considered.
- The GITSG conducted a multi-institutional, randomized, three-arm study comparing 60 Gy radiation with combination 5-FU and radiation (given at either 40 or 60 Gy) in 194 patients [38]. Chemoradiation was delivered as previously described with radiation to 40 or 60 Gy. Median survival was significantly improved in the two combined-modality arms compared with radiation alone (42 and 40 weeks vs 23 weeks, $P < 0.01$). Toxicity—predominantly myelosuppression—was more pronounced in the combined-modality arms.
- Another small GITSG study evaluated the role of chemotherapy alone by randomizing 43 patients to one of two arms: SMF chemotherapy (streptozocin, mitomycin and 5-FU) or SMF combined with external beam radiation [39]. Median survival was modestly improved for the combined treatment group (42 vs 32 weeks, $P < 0.02$). Gastrointestinal and hematologic toxicity was greater on the combined treatment arm.
- The authors prefer a continuous infusion of 5-FU throughout radiation to maximize radiosensitization. Multi-agent chemotherapy has not been shown to offer an additional benefit over 5-FU alone.
- Gemcitabine alone is acceptable therapy in patients unable to tolerate combined modality therapy.
- Ongoing trials are evaluating the feasibility and efficacy of combining gemcitabine with radiation in locally advanced disease.

Chemoradiation for locally advanced disease

Standard dosage	Similar to adjuvant regimen.
Contraindications	Poor nutritional or performance status, surgically resectable disease, distant metastases, prior radiation therapy, inflammatory bowel disease, scleroderma, systemic lupus erythematosus, significant renal insufficiency.
Main drug interactions	Similar to adjuvant regimen.
Main side effects	Similar to adjuvant regimen.
Special points	Adequate performance status is essential (Eastern Cooperative Oncology Group ≤ 2). Patients should be encouraged to enter clinical trials.

Therapy for metastatic disease

- Chemotherapy is the primary treatment modality for metastatic disease because these patients generally do not benefit from palliative surgical resection (see above for surgical palliation of jaundice/obstruction), or routine incorporation of radiation therapy.
- Prior to the development of gemcitabine, 5-FU–based regimens resulted in response rates of less than 10%, without clear impact on survival. Multiagent regimens did not improve outcome compared with single-agent 5-FU [40].
- Burris *et al.* [36•] conducted a randomized, multicenter trial comparing gemcitabine to weekly 5-FU bolus therapy in 126 patients. Patients receiving gemcitabine showed significant but modest improvements in both median survival (5.6 vs 4.4 months, $P = 0.0025$) and 1-year survival (18% vs 2%, $P = 0.0025$), despite objective response rates of 5% and 0% for gemcitabine and 5-FU, respectively.

- In the Burris trial, 24% of patients treated with gemcitabine compared with 5% of 5-FU–treated patients were classified as clinical benefit responders, as assessed by improvement in pain scores, performance status, and maintenance of weight.
- Currently, the standard treatment for metastatic pancreatic cancer is gemcitabine. Beacuse the prognosis for these patients remains dismal, enrollment in a clinical trial of novel therapy should be considered as initial therapy.

Gemcitabine

- Gemcitabine is a nucleoside analogue that requires intracellular phosphorylation for activation. It inhibits DNA synthesis by becoming incorporated into DNA and terminating DNA chain elongation. It reduces intracellular deoxynucleoside triphosphates through its inhibition of ribonucleotide reductase.

Standard dosage 1000 mg/m² intravenously over 30 minutes. Given weekly for first 7 weeks followed by 1 week rest, then 3 weeks out of 4.

Contraindications Poor performance status, hepatic insufficiency.

Main drug interactions No common interactions.

Main side effects Myelosuppression, flulike symptoms (fever), rash, mild nausea/vomiting, hemolytic-uremic syndrome (rare), noncardiogenic pulmonary edema (rare), peripheral edema.

Symptom management

- Patients with pancreatic cancer frequently suffer debilitating symptoms. Recognition of these problems and attention to palliative care is an essential component of patient management.
- Pain is frequently associated with pancreatic cancer, reported by 30% to 60% of patients with early disease and more than 80% of those with advanced disease [41]. Patients typically describe an intermittent or constant abdominal discomfort that can radiate to the back. Pharmacologic management should be the first step, following the World Health Organization escalating three-step analgesic ladder [42]. If pain is unrelieved with analgesics, celiac plexus chemical splanchnicectomy can provide substantial pain relief. Nerve blockade may also be considered at the time of surgical exploration. Additionally, radiation therapy can serve to palliate pain symptoms.
- Depression often accompanies pancreatic cancer and should be treated aggressively, with consideration given to both pharmacologic and psychosocial interventions. Kelsen *et al.* [43] found that 38% of patients with pancreatic cancer set to undergo their first treatment had significant depressive symptomatology.
- Malnutrition is common in pancreatic cancer patients. Wigmore *et al.* [44] reported that patients had lost a median of 14.2% of their pre-illness weight at diagnosis, and 24.5% at subsequent assessment. Because it is difficult to correct malnutrition after it has progressed, anticipation of this problem and early consultation with a nutritionist are essential to evaluate specific patient needs. The routine use of total parenteral nutrition is not recommended due to the poor short-term prognosis in these patients.
- Painless jaundice is a hallmark sign of pancreatic cancer. Methods for decompressing biliary obstruction have been discussed earlier and include endoscopically placed stents, percutaneously placed stents, and intraoperative biliary bypass. The particular method chosen depends on the patient's clinical status.

Emerging therapies

- Given the high mortality rate associated with pancreatic cancer, the development of novel treatment approaches is essential.
- Phase I and II studies are ongoing to evaluate the combination of gemcitabine with radiation in both the neoadjuvant and adjuvant settings. A current Intergroup Phase III trial is comparing gemcitabine versus 5-FU before and after 5-FU–based chemoradiation in the adjuvant setting.
- Advances in understanding pancreatic cancer tumor biology have led to exploration of other approaches targeting cell growth (*eg*, growth factor receptors and signal transduction pathways) and host–tumor interactions (*eg*, angiogenesis). A signal transduction pathway target of great interest involves mutant RAS, which is present in greater than 90% of pancreas cancers. The use of vaccines and small molecules to exploit this tumor-specific target is being actively pursued.

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