Cancer Management Chapter 11: Pancreatic, neuroendocrine GI, and adrenal cancers

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By Al B. Benson III, MD, FACP [1], Robert J. Myerson, MD, PhD [2], and Aaron R. Sasson, MD [3]

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PANCREATIC CANCER

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Incidence and epidemiology

**Gender**
The incidence of pancreatic cancer is slightly higher in males than in females. These gender differences are most prominent among younger individuals.

**Age**
The peak incidence of pancreatic carcinoma occurs in the seventh decade of life. Two-thirds of new cases occur in people > 65 years old.

**Race**
The incidence of pancreatic cancer is higher in the black population, with an excess risk of 40% to 50% over that in whites. Perhaps more importantly, black males probably have the highest risk of pancreatic cancer worldwide.

**Survival**
Cancer of the pancreas is a highly lethal disease historically, with few reports of 5-year survivors. However, more recent series have shown a decrease in both operative mortality and overall morbidity. There has also been a significant increase in 5-year survival after curative resection (21%–25%). Factors that appear to be important in predicting long-term survival after resection include clear surgical margins, small tumor size (< 2 cm), negative lymph nodes, and reduced perioperative mortality.
Adenocarcinoma of the pancreas, the most common histologic type, has a median survival of 9 to 12 months and an overall 5-year survival rate of 3% for all stages. At the time of diagnosis, over 50% of patients with pancreatic adenocarcinoma have clinically apparent metastatic disease. Among patients whose disease is considered to be resectable, 50% will die of a recurrent tumor within 2 years.

**Etiology and risk factors**
The specific risk factors for pancreatic cancer are not as striking as those for other gastrointestinal (GI) malignancies, such as esophageal and gastric carcinomas. There does, however, appear to be a significant relationship between pancreatic cancer and environmental carcinogens.

**Cigarette smoking**
Cigarette smoke is one of the carcinogens directly linked to the causation of pancreatic malignancies. Heavy cigarette smokers have at least a twofold greater risk of developing pancreatic carcinoma than nonsmokers. In Japan, cigarette smoking carries an even greater risk, which can be as much as 10-fold in men smoking one to two packs of cigarettes daily.

**N-nitroso compounds**
These compounds, found particularly in processed meat products, reliably induce pancreatic cancer in a variety of laboratory animals. No study has directly linked dietary carcinogens to pancreatic cancers in humans.
Caffeine
The contribution of caffeine consumption to the development of pancreatic carcinoma is controversial. A case-controlled study showed a correlation between caffeine consumption and pancreatic cancer. However, other studies have been unable to confirm this relationship.

Alcohol
A clear-cut relationship between alcohol use and pancreatic carcinoma has not been shown.

Diabetes
Hyperglycemia does not seem to be a risk factor for pancreatic cancer. However, 10% of all patients with pancreatic carcinoma present with new-onset diabetes.

Genetic factors
Cancer of the pancreas is a genetic disease. To date, more than 80% of resected pancreatic cancers have been found to harbor activating point mutations in KRAS. In addition, the tumor-suppressor genes CDKN2A, TP53, and DPC4 are all frequently inactivated in this cancer.

Research is also focusing on aberrantly methylated genes in pancreatic cancer using methylation-specific polymerase chain reaction and the identification of microRNAs as targets for detection strategies.

Familial pancreatic carcinoma has been associated with the following genetic syndromes: hereditary pancreatitis, ataxia-telangiectasia, hereditary nonpolyposis colorectal cancer, familial atypical mole melanoma syndrome, Peutz-Jeghers syndrome, and familial breast cancer. Families with CDKN2A germline mutations may be at higher risk of developing pancreatic cancer than those without these mutations.

Signs and symptoms
The initial clinical features of pancreatic carcinoma include anorexia, weight loss, abdominal discomfort or pain, and new-onset diabetes mellitus or thrombophlebitis. The vague nature of these complaints may delay diagnosis for several months.

Pain
Specific symptoms usually relate to localized invasion of peripancreatic structures. The most common symptom is back pain, which stems from tumor invasion of the splanchnic plexus and retroperitoneum or pancreatitis. This pain is described as severe, gnawing, and radiating to the middle of the back. Pain can also be epigastric or in the right upper quadrant if bile duct obstruction is present.

Jaundice
In a majority of cases, patients also may present with jaundice. Painless or, sometimes, painful jaundice occurs when lesions involve the intrapancreatic bile duct.

GI symptoms
Tumor invasion of the duodenum or gastric outlet may give rise to nausea or vomiting as a presenting symptom. This symptom is rare early in the course of the disease. Changes in bowel habits related to pancreatic insufficiency may also be present, along with associated steatorrhea.

Glucose intolerance
Recent onset of glucose intolerance associated with GI symptoms in an elderly patient should alert physicians to the possibility of pancreatic carcinoma.

A palpable gallbladder
When it occurs without cholecystitis or cholangitis, a palpable gallbladder suggests malignant obstruction of the common bile duct until proven otherwise. This so-called Courvoisier’s sign is present in about 25% of all patients with pancreatic cancer.

Other physical findings include Trousseau’s syndrome (migratory superficial phlebitis), ascites, Virchow’s node (left supraclavicular lymph node), or a periumbilical mass (Sister Mary Joseph’s node).

Screening and diagnosis
Early diagnosis of pancreatic carcinoma is difficult but essential if surgical resection and cure are to be improved. Defining early lesions at a resectable stage remains a diagnostic challenge. To date, leading medical organizations have not recommended routine screening of asymptomatic individuals for pancreatic cancer.

Serum markers
The use of serologic tumor markers such as CA19-9 for pancreatic carcinoma, was originally thought to be appropriate as a screening tool. However, since the prevalence of pancreatic carcinoma in the
general population is extremely low (0.01%), many false-positive screening results are generated. Also, the sensitivity of CA19-9 is not high (20%) in stage I cancers. Nevertheless, CA19-9 may be a useful marker for diagnosing patients at high risk who have appropriate symptoms; such individuals include smokers, recent-onset diabetics, those with familial pancreatic cancer, or those with unexplained weight loss or diarrhea. This marker correlates with tumor burden and is useful in following disease and in assessing the adequacy of resection or therapy. CA19-9 should be interpreted with caution in patients, who have jaundice, as it is falsely elevated in such patients. Furthermore, 5% to 15% of the population are unable to synthesize CA19-9; in such patients, levels of this marker would be falsely low, even in the presence of extensive tumor burden.

No currently available serum marker is sufficiently accurate to be considered reliable for screening asymptomatic patients.

**Laparoscopy**  
This diagnostic is useful for staging patients with pancreatic carcinoma and for formulating treatment plans. Approximately 10% to 15% of patients thought to have resectable disease are found to have distant metastases at laparoscopy. The false-negative rate of laparoscopy is <10%. The strongest indications for laparoscopy are locally advanced disease and tumors of the body and tail of the pancreas.

**Peritoneal cytology**  
This technique also is being explored for the diagnosis of pancreatic carcinoma. Cytology is positive in 5% to 10% of patients who are thought to have localized disease. There are anecdotal cases of long-term survival after resection where positive cytology of peritoneal washings was noted, but the clinical/prognostic value of this test is not yet known. However, there is increasing evidence that the presence of positive peritoneal cytology is a marker of advanced disease, and curative resection is extremely unlikely.

**Imaging techniques**  
Imaging for pancreatic carcinoma is best performed with conventional ultrasonography and CT.

**Ultrasonography**  
The limit of sonographic resolution for early pancreatic carcinoma is a diameter of 1.0 to 1.5 cm. A mass located in the pancreatic head will produce dilatation of the common bile duct and pancreatic duct. The actual sensitivity of ultrasonography in the diagnosis of pancreatic carcinoma is ~70%.

**CT**  
This diagnostic provides better definition of the tumor and surrounding structures than does ultrasonography and is operator-independent. CT correctly predicts unresectable tumors in 85% of patients and resectable tumors in 70% of patients. Findings of tumor unresectability on CT scanning include distant lymphadenopathy, encasement or occlusion of the superior mesenteric artery (SMA) or celiac artery, occlusion of the portal vein or superior mesenteric vein (SMV), and distant metastases. Spiral CT increases the accuracy of detecting pancreatic carcinoma in general and vessel encasement in particular. This technique permits rapid data acquisition and computer-generated three-dimensional (3D) images of the mesenteric arterial and venous tributaries in any plane. Spiral CT is quicker and less expensive than angiography and uses less contrast medium.

**PET**  
The use of positron emission tomography with 18fluorodeoxyglucose (FDG-PET) in the evaluation of patients with pancreatic cancer is expanding. A recent study of 126 patients with focal, malignant, or benign pancreatic lesions showed high sensitivity of FDG-PET for detection of small pancreatic neoplasms. Lack of focal glucose uptake excludes pancreatic neoplasms (sensitivity, 85.4%; specificity, 60.9%).

**Magnetic resonance imaging (MRI)**  
At present, MRI is not as accurate as CT in diagnosing and staging pancreatic carcinoma. MRI may be as useful as CT in staging and can provide magnetic resonance angiography and magnetic resonance cholangiopancreatography (MRCP) images if needed. As yet, MRCP is not a standard test for the diagnosis of pancreatic carcinoma, but it may become helpful in the future.

**Endoscopic ultrasonography (EUS)**  
This test is a newer modality for the diagnosis of pancreatic carcinoma, that offers an overall diagnostic accuracy rate of approximately 85% to 90%. For the assessment of regional lymph node metastases, the accuracy of EUS is 50% to 70%. This technique is also important in the evaluation of portal vein/SMV involvement by tumor. EUS-guided fine-needle cytology of periampullary tumors may yield new information with respect to the diagnosis of pancreatic cancer. Further, this technique
may pose less risk of spreading cells by needle tracking than does percutaneous biopsy. In a comparison of EUS and spiral CT, both techniques showed comparable efficacy in detecting tumor involvement of lymph nodes and the SMVs and portal veins. However, EUS is less helpful in the evaluation of the SMA.

Recently, some investigators have expressed interest in using EUS to screen high-risk patients, individuals with defined genetic syndromes, and those with a strong family history of pancreatic cancer for evidence of the disease. In a recent study of 78 high-risk patients, screening showed neoplastic changes in 10% of the subjects. However, the challenge of EUS is the current inability to detect malignant precursor lesions, known as PanIN.

**Endoscopic retrograde cholangiopancreatography (ERCP)**

This technique may someday be supplanted as a diagnostic tool by EUS, although ERCP presently is used in many clinics. Also, if a patient presents with jaundice and the CT scan reveals dilatation of the common bile duct without an obvious mass, ERCP may be complementary to spiral CT. ERCP findings of pancreatic cancer include an abrupt or tapered cutoff of either or both the main pancreatic and common bile ducts.

### Pathology

**Adenocarcinoma**

This type of tumor, arising from the exocrine gland ductal system, is the most common type of pancreatic cancer, accounting for 95% of all cases. Two-thirds of these cancers originate in the pancreatic head, and the remainder arise in the body or tail. Most ductal carcinomas are mucin-producing tumors and usually are associated with a dense desmoplastic reaction. Although most pancreatic adenocarcinomas arise from the ductal epithelium, pancreatic acinar carcinomas and cancers arising from mucinous cystic neoplasms are also found.

**Multicentricity,** which is usually microscopic, is not unusual.

**Metastatic spread** Perineural invasion occurs in the majority of patients with pancreatic carcinoma. In addition, pancreatitis distal to and surrounding the tumor is usually present. Most patients present with lymph node metastases in the region of the pancreaticoduodenal drainage basins. The subpyloric and inferior pancreatic head, SMA, and para-aortic lymph node groups also may be involved. Distant metastatic spread most commonly involves the liver and peritoneal surfaces.

**Staging and prognosis**
Pancreatic adenocarcinoma is staged according to local spread of disease, nodal status, and distant metastatic involvement using the AJCC TNM system (Table 1). The T staging of the primary tumor includes an analysis of direct extension of disease to the duodenum, bile duct, or peripancreatic tissues. A T4 advanced cancer may extend directly to the SMA or celiac axis, meaning that the cancer is unresectable.

**Independent prognostic factors**

Lymph node metastases and tumor size and differentiation have independent prognostic value in patients with pancreatic carcinoma. Significantly improved survival is seen in patients with smaller lesions, lymph node-negative tumors, and tumors in which the surgical margins are not involved.

![Lymph node and margin status](image)

Prior to the age of adjuvant therapy, lymph node status was the most dominant prognostic factor (Figure 1). It is now rivaled by surgical margin status in series where surgical margins have been meticulously examined.

**Treatment**

**Surgical treatment of resectable disease**

The rate of resection for curative intent ranges from 10% to > 75%, with the higher percentage resulting from both a more aggressive approach and better preoperative staging for resectability. Also, there is growing evidence that patients with potentially resectable pancreatic cancer have a shorter hospital stay, reduced surgical mortality, and an overall better outcome if the surgery is performed at “high-volume” medical centers staffed by experienced surgeons (approximately 16 operable cases per year).

Extended resections may include portal or superior mesenteric vessels, the colon, the adrenal glands, or the stomach. If resection of adjacent organs or tissues results in the conversion of a positive to a negative resection margin, it is of great potential benefit to the patient. With regard to the extent of lymph node dissection, several recent, prospective, randomized studies have shown an increase in postoperative morbidity, but with no improvement in overall survival in patients undergoing an extended lymph node dissection.

**Determination of resectability**

The initial approach to surgery for pancreatic carcinoma includes a determination of resectability. This determination should be first made preoperatively with high-quality CT or MRI and, perhaps, EUS. Operative determination of resectability includes careful examination of the liver, porta hepatis, and portal and superior mesenteric vessels. The head of the pancreas and uncinate process are mobilized by an extensive Kocher maneuver to evaluate the head of the pancreas. The SMA is palpated, and its relationship to the tumor is assessed. The hepatic artery and celiac trunk are examined to make certain there is no vascular encasement. Currently, pancreatic lesions may be classified as resectable, borderline resectable, and unresectable. Indicators of borderline resectable tumors include impingement or abutment on the SMV/porta vein, short segment venous occlusion with a suitable proximal and distal vein for reconstruction, minimal involvement of the gastroduodenal artery and hepatic artery, and < 180° involvement of the SMA. Criteria for unresectability include detection of distant metastases and circumferential involvement of the SMA, hepatic artery, or celiac artery.

**Operative intervention**

**Intraoperative biopsy** Most patients with resectable periampullary tumors can successfully undergo pancreaticoduodenectomy without an intraoperative biopsy. A time-consuming frozen
section interpretation may not be informative, and histologic confirmation may be impossible with small lesions associated with peritumoral pancreatitis. Most large series of pancreaticoduodenectomy for carcinoma include resections of benign pathology based on clinical judgment. A negative fine-needle cytology should not deter an experienced surgeon from proceeding with resection.

**Whipple vs pylorus-preserving procedure**  If the tumor is deemed to be resectable, a standard pancreaticoduodenectomy (Whipple procedure) or pylorus-preserving Whipple procedure (PPW) is performed. The PPW theoretically eliminates the nutritional problems caused by a reduced gastric reservoir and gastric dumping, but this finding has not been shown to alter long-term nutritional status. If there is any doubt about cancer proximity or blood supply to the pylorus, an antrectomy should be performed. If the tumor approaches the pylorus or involves the subpyloric nodes, classic antrectomy is preferred. Recent prospective randomized studies have shown there to be no significant difference between pylorus-preserving and standard Whipple resection.

**Reconstruction technique**  The most common reconstruction technique after a Whipple resection requires a single retrocolic jejunal loop to complete the pancreaticojejunostomy, which is followed by a cholangiojejunostomy and gastrojejunostomy. A duct-mucosal anastomosis is preferred to the pancreaticojejunostomy. Pancreaticogastrostomy is also an effective and safe means of creating the anastomosis.

**Postoperative complications**  Operative mortality of pancreaticoduodenectomy is currently < 6% in major surgical centers. The leading causes of postoperative mortality include postoperative sepsis, hemorrhage, and cardiovascular events. Most of the septic complications arise from pancreaticojejunostomy leaks.

In many series, early delayed gastric emptying is the leading cause of morbidity for pylorus-preserving procedures. The number-two cause of morbidity, seen in 5% to 15% of all patients, is a leak or fistula from the pancreatic anastomosis. Today, with appropriate drainage and nutritional support, more than 95% of pancreatic fistulas will heal using conservative measures.

An analysis of 200 patients who underwent resection of pancreatic adenocarcinoma in the era prior to adjuvant therapy found that the most important factors influencing long-term survival were the diameter of the primary tumor, status of the resected lymph nodes, and status of the resected margins. Patients with tumors < 3 cm in diameter had significantly longer median survival and 5-year survival rates (21 months and 28%, respectively) than those with tumors ≥ 3 cm (11.5 months and 15%). Patients with no lymph node involvement had a 5-year survival rate of 36%, as compared with < 5% for those with positive nodes. Patients who underwent resections with negative margins had a 5-year survival rate of 26%, versus 8% for those with positive margins. The type of resection (pylorus-preserving vs standard Whipple procedure) did not influence survival.

**Body and tail tumors**  Tumors in the body and tail of the pancreas are typically larger than tumors in the head of the pancreas and are often metastatic upon presentation. For those patients who are surgical candidates, resection employs a distal pancreatectomy with concomitant splenectomy. Due to their large size, removal may require resection of adjacent organs. Of note, the rate of pancreatic leaks following distal pancreatectomy is approximately 30% to 40%, although, with appropriate treatment, they resolve using conservative measures.

**Surgical palliation**  Surgical palliation is also considered in patients undergoing exploration with curative intent. Jaundice, gastric obstruction, and pain may be alleviated by surgical palliation.

**Biliary tract obstruction**  Either a choledochojejunostomy or cholecystojejunostomy can be used to bypass the biliary obstruction. Recurrent jaundice and cholangitis are less likely to develop when the common duct is used for decompression.

**Duodenal obstruction**  Although duodenal obstruction is rare as a presenting symptom, duodenal involvement may occur eventually in 25% of patients. Some investigators believe that prophylactic bypasses are safe and should be performed in all patients. One phase III trial supports prophylactic bypass, but the subject remains controversial.

**Pain relief**  Severe back pain may be an incapacitating symptom. Pain relief may be achieved by chemoablation of the celiac plexus or by alcohol injection, which may be performed intraoperatively, percutaneously, or endoscopically. An intraoperative injection of 25 mL of ethanol (95%) on both sides of the celiac axis will ablate tumor pain. (For further discussion of these techniques, see
chapter 34 on “Pain Management.”

**Neoadjuvant and adjuvant therapies**

**Radiation therapy**

Even with apparently adequate surgical resection, pancreatic cancer has a high risk of locoregional recurrence. Moreover, most lesions are unresectable, even when there is no apparent distant metastatic disease. Thus, there is a theoretical rationale for the adjunctive use of radiation therapy, either before or after surgery, in almost all patients. Preoperative (neoadjuvant) radiation therapy may help render locally advanced lesions resectable with negative margins (R0 resection). Postoperative (adjuvant) radiation therapy may help eliminate suspected residual microscopic disease in the tumor bed and/or regional lymphatics. Alternative radiation techniques, including intensity-modulated radiotherapy and 3D conformal radiation therapy, are being explored. With an effective chemotherapeutic agent, there is greater potential for adequate locoregional cytotoxicity—as well as control of subclinical distant disease—that could be obtained with limited doses of adjuvant radiation therapy alone.

**Preoperative chemoradiation therapy**

Several single-institution studies have evaluated the role of preoperative irradiation in conjunction with fluorouracil (5-FU)- and gemcitabine (Gemzar)-based chemotherapy. In these studies, 60% to 80% of the lesions were completely resected 1.0 to 1.5 months after the completion of chemoradiotherapy. Median survival has ranged from 16 to 36 months, but no phase III trials have been conducted to evaluate preoperative therapy versus postoperative sequencing. A RTOG/SWOG/ECOG intergroup trial, the largest of its kind, compared infusional 5-FU with gemcitabine. Each agent was given before and after chemoradiotherapy in patients with resected pancreatic cancer. Radiation therapy was administered without a treatment break and was given with continuous-infusion 5-FU in both arms. The study accrued 451 patients and demonstrated a survival advantage for patients with pancreatic head adenocarcinoma who received gemcitabine vs those treated with 5-FU (median overall survival 20.5 vs 16.9 months; \( P = .033 \)).

Further analysis of this trial suggests that postresection CA 19-9 levels serve as a surrogate marker for residual disease. Patients with a postresection CA 19-9 level > 180 IU/mL had a median survival of 9 months as compared with 21 months for those having a CA 19-9 level < 180 IU/mL (\( P < .001 \)). Furthermore, use of a CA 19-9 cutoff of 90 IU/mL, as employed in the German CONKO trial, resulted in a median survival of 23 months—a rate similar to that noted in the CONKO trial (Berger A, et al: J Clin Oncol 20:5918–5922, 2008).

Preoperative radiation therapy, to 4,500 to 5,000 cGy, in conjunction with chemotherapy should be considered for patients with pancreatic adenocarcinoma who are medically fit but who have marginally resectable disease. There are research initiatives to further address the role of neoadjuvant chemotherapy. For example, phase II studies explore high-dose gemcitabine and high-dose gemcitabine and cisplatin with short-term radiation therapy for locally advanced cancer. Other neoadjuvant strategies include the addition of oxaliplatin (Eloxatin), bevacizumab (Avastin), cetuximab (Erbitux), or erlotinib (Tarceva) to gemcitabine/irradiation combinations.

**Postoperative chemoradiation therapy**

A total of 541 patients were enrolled in a trial conducted by the ESPAC. This study evaluated the benefits of adjuvant therapy. The design was complex, attempting to assess several options. It included no further therapy after surgery, chemoradiation therapy (bolus 5-FU with split-course radiotherapy), chemotherapy (5-FU with leucovorin), and chemoradiation therapy followed by chemotherapy.

Interpretation of the results is confounded by the fact that some institutions opted for a full 2 × 2 randomization (all four options), whereas others allowed only two options (no further therapy vs chemotherapy or no further therapy vs chemoradiation therapy). Patients receiving these two options could also have therapy other than that prescribed in the randomization. Furthermore, no data were collected regarding time to disease recurrence or whether treatment was given after recurrence. Curiously, the median survival of those in the control group was more than 17 months—much longer than those of the control groups from the GITSG and EORTC trials. Only the 5-FU-with-leucovorin arm would be considered a state-of-the-art approach, and it was demonstrated to improve survival significantly (\( P = .0005 \)). This finding would suggest a strong benefit to postoperative chemotherapy. If radiation therapy is included, it would probably best be given after 1 to 2 months of full-dose chemotherapy. Most practitioners would recommend continuous-course radiation therapy rather than split-course treatment. In contrast to the recent RTOG trial, however, the ESPAC trial paid no attention to radiotherapeutic quality control. A German
randomized phase III trial including 368 patients with resected pancreatic cancer compared postoperative gemcitabine given for 6 months with observation. Disease-free survival was significantly superior for patients receiving postoperative gemcitabine (13.4 months vs 6.9 months; \( P < .001 \)), including for patients with either R0 or R1 resection. Overall survival, however, was not significantly different between the gemcitabine and control groups (22.1 months vs 20.2 months; \( P = .06 \); Oettle H, et al: JAMA 297:267–277, 2007). In an updated analysis, the benefits of gemcitabine as compared with observation remained. Despite an improvement in median survival of only 2 months noted among treated patients (22.8 months vs 20.2 months; \( P = .005 \)), a 5-year survival of 21% in the treatment arm versus 9% in the observation arm was reported (Neuhaus P, et al: J Clin Oncol 26[15S]: abstract LBA4504, 2008).

The ACOSOG Z05031 trial was a phase II trial that tested a regimen of radiation therapy, cisplatin, interferon-alfa, and 5-FU in patients with resected pancreatic cancer. The trial demonstrated a median survival of 27.1 months, which was the longest survival reported with use of adjuvant therapy in a cooperative group trial. However, use of this regimen was associated with significant toxicity, and only 56% of patients completed the entire treatment course. In addition, the GI Intergroup is conducting a randomized phase II trial to explore new combinations incorporating the monoclonal antibodies bevacizumab and cetuximab, each given with gemcitabine; irradiation is given with oral capecitabine (Xeloda). A systematic review of 11 trials including 794 patients with locally advanced pancreatic cancer using radiation/combined-modality therapy showed a survival benefit for chemoradiation over irradiation alone, but there was not a significant advantage for chemoradiation followed by chemotherapy compared with chemotherapy alone (Sultana A, et al: Br J Cancer 96:1183–1190, 2007).

**Locally advanced but potentially resectable lesions**

These lesions comprise 10% to 15% of cases presenting to physicians. Data from phase II preoperative chemoradiotherapy trials indicate that trinodality therapy is crucial for margin-free resection and long-term survival. A meta-analysis from the ESPAC1 trial showed that chemotherapy alone is ineffective for patients having had resection for microscopic disease at a margin (R1) thus adding further support to both chemotherapy and radiation therapy for these borderline resectable patients will be mounting a trial with preoperative capecitabine, bevacizumab, and radiation therapy for these patients.

**Treatment of unresectable lesions**

**Irradiation**

Radiation therapy can prolong and/or improve quality of life in some patients with unresectable adenocarcinoma of the pancreas. It is better combined with chemotherapy. Long-term survival is, unfortunately, highly unusual. The results of ESPAC 3, a multi-center trial comparing adjuvant 5-FU/leucovorin versus gemcitabine in patients with a resected pancreatic adenocarcinoma, was recently presented at ASCO 2009. Following R0/R1 resection, patients were randomized to 5-FU (425 mg/m²) bolus on days 1-5 every 28 days versus gemcitabine (1,000 mg/m²) given intravenously on days 1, 8, and 15 every 4 weeks. Both regimens were continued for 6 months. A total of 1,088 patients were randomized and after a minimum of two years follow-up, median survival for the 5-FU/leucovorin group was 23 months compared to 23.6 months for the gemcitabine group. There was no statistical significance between the two study arms (Neoptolemos J et al: J Clin Oncol 27[18S]: abstract LBA4505, 2009).

**Chemoradiation**

The addition of chemotherapy to radiation therapy has been shown to improve the survival of patients with unresectable pancreatic adenocarcinoma, with moderate doses of radiation only slightly less effective than higher doses. In a GITSG trial of unresectable disease, moderate-dose radiation (4,000 cGy) with 5-FU chemotherapy significantly improved survival, as compared with higher doses of radiation (6,000 cGy) and no chemotherapy (median survival, 9.6 vs 5.2 months). The GITSG has also compared chemotherapy plus irradiation with chemotherapy alone and demonstrated a significant improvement with combined-modality therapy (median survival, 42 vs 32 weeks).

Based on these data, except in a protocol setting, the palliative management of a patient with unresectable pancreatic adenocarcinoma who has significant local symptoms should probably consist of moderate doses of radiation (4,000–5,000 cGy) in conjunction with 5-FU-based...
chemotherapy. As in adjuvant treatment, carefully shaped portals approximately 12 × 12 cm should be used. Many practitioners would favor several months of gemcitabine-based chemotherapy before proceeding to radiotherapy and 5-FU for patients experiencing no substantial local symptoms. This allows early delivery of optimal chemotherapy and spares the patient destined to rapid dissemination of disease from the morbidity associated with use of 5-FU plus radiotherapy. The ECOG conducted a randomized, prospective trial in patients with locally advanced, unresectable, nonmetastatic pancreatic adenocarcinoma. Patients were randomized to receive either gemcitabine monotherapy or radiation therapy given concurrently with and followed by gemcitabine. The overall survival was 11 months in the combination-therapy group and 9.2 months in the chemotherapy-only group (P = .034). Despite the statistical significance of these findings, this trial was plagued by poor accrual and was terminated early (Loehrer P et al: J Clin Oncol 26[155]: abstract 4506, 2008).

Approaches under investigation At present, clinical investigators are investigating a variety of chemoradiation therapy approaches. The radiosensitizing properties of the biologic agents, including cetuximab, bevacizumab, and erlotinib, are being explored in radiation therapy clinical trials in combination with chemotherapy. Trials with combined gemcitabine and irradiation are of particular interest due to the activity of this drug in pancreatic cancer and the fact that it is a potent radiosensitizer. The benefit of irradiation for patients with locally advanced disease, however, remains a research question because of toxicity concerns and the relatively brief survival rates. If gemcitabine is given either before or after a course of radiation therapy, full doses of 1,000 mg/m² are possible. If irradiation and gemcitabine are given concurrently, doses of either modality must be sharply reduced. A phase II trial combined “full-dose” gemcitabine (1,000 mg/m²) with radiation therapy directed at the primary tumor alone (36 Gy). Therapy was well tolerated. Among 39 treated patients, disease was controlled in 84.6% and CA 19-9 levels were reduced significantly. One-year survival was 73% for all patients and was significantly better for resectable patients (94%) than for those considered to be borderline-resectable (76%) or unresectable (47%). Three Intergroup metastatic pancreatic trials have been reported. The ECOG completed a trial of gemcitabine vs fixed-rate infusion gemcitabine vs fixed-rate gemcitabine plus oxaliplatin, accruing 832 patients. At a median follow-up of 12.2 months, neither of the two investigational regimens was significantly better than standard gemcitabine (both only had approximately 1 month longer median survival) (Poplin E et al: J Clin Oncol 27:3778-3785, 2009). The CALGB compared bevacizumab plus gemcitabine with gemcitabine alone, finding no difference between the regimens (Kindler H et al: J Clin Oncol 25[18S]:abstract 4508, 2007). The SWOG trial evaluated gemcitabine with or without cetuximab. The study reported no difference in outcome (Philip PA, et al: J Clin Oncol:abstract LBA4509, 2007).

The dose of gemcitabine that can be given concurrently with irradiation depends on the volume and dose of radiation. If full doses of gemcitabine (1,000 mg/m²/wk) are given concurrently with irradiation, the dose of radiation must be markedly reduced to avoid unacceptable GI toxicity.

Treatment of metastatic adenocarcinoma Pancreatic adenocarcinoma is still one of the most frustrating, resistant solid neoplasms to treat, and therapy for metastatic disease remains palliative. Few agents have demonstrated activity in > 10% of patients diagnosed with this disease. Moreover, most of the reported series have been small, and not all encouraging results have been duplicated.

Chemotherapy As metastatic pancreatic carcinoma is incurable, the anticipated risks of chemotherapy, which are often substantial, must be balanced against the gains that may be achieved; unfortunately, these are few. Patients who are debilitated due to their underlying or comorbid disease should not be offered chemotherapy, as their likelihood of deriving any benefit is exceedingly slim. However, patients who desire therapy and who, while symptomatic, still have a good performance status may be offered “standard” chemotherapy (Table 2), or, if possible, they should be encouraged to participate in a clinical trial. The NCIC has presented a randomized phase III study comparing gemcitabine with or without erlotinib in 530 patients with metastatic pancreatic cancer. The combination produced improvement in both overall (6.24 vs 5.91 months; hazard ratio [HR]:0.82; P = .038) and progression-free survival (HR:0.77; P = .007). As with other epidermal growth factor receptor–targeted agents, skin rash was associated with response. Diarrhea was increased with the combination (Moore MJ, et al: J Clin Oncol 25:1960-1966, 2007).

5-FU Historically, single-agent 5-FU has been associated with a response rate of 25% in pancreatic cancer. The use of 5-FU, doxorubicin, and mitomycin (FAM) and 5-FU plus doxorubicin offer no
advantage over 5-FU alone. 5-FU plus leucovorin appears to be ineffective. **Gemcitabine** is indicated for the treatment of locally advanced or metastatic pancreatic adenocarcinoma. Gemcitabine was compared with 5-FU in a group of 126 previously untreated patients and showed a small, but statistically significant, improvement in response rate. Median survival in the gemcitabine group was 5.7 months, with 18% of patients alive at 12 months, as compared with 4.4 months in the group receiving 5-FU, with 2% of patients alive at 12 months. Perhaps more importantly, clinical benefit response (a composite measurement of pain, performance status, and weight) occurred in 23.8% of the gemcitabine-treated group, as compared with 4.8% of the 5-FU-treated group. Due to its palliative potential, gemcitabine has become the standard of care for patients with resectable pancreatic adenocarcinoma.

**Combination therapy** There have been a number of attempts to improve the therapeutic outcome for patients with metastatic pancreatic cancer by comparing promising combinations of agents in randomized clinical trials. Unfortunately, the results have been disappointing. The ECOG compared gemcitabine with or without 5-FU, demonstrating a median survival of 5.4 months for gemcitabine versus 6.7 months for the combination; however, this difference was not statistically significant. Another trial explored the addition of irinotecan to gemcitabine. There was no survival benefit when this regimen was compared with gemcitabine alone, although the combination did increase the tumor response rate (16.1% vs 4.4%; \( P < .001 \)). A meta-analysis of 15 randomized trials showed a significant survival benefit for patients with advanced pancreatic cancer and a good performance status who received gemcitabine either with a platinum analog (hazard ratio [HR]: 0.85; \( P = .01 \)) or a fluoropyrimidine (HR: 0.9; \( P = .03 \)). A European randomized trial for 319 patients with advanced pancreatic cancer compared capecitabine plus gemcitabine vs gemcitabine alone and showed no difference in overall survival (8.4 vs 7.2 months; \( P = .234 \)). The combination showed improved median overall survival in good performance status patients (10.1 vs 7.4 months; \( P = .014 \)). (Herrmann R, et al: J Clin Oncol 25:2212–2217, 2007).

Preliminary results from a randomized phase II trial comparing folfirinox–5-FU/leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) versus gemcitabine for 88 patients with metastatic pancreatic cancer showed response rates of 38.7% versus 11.7%, respectively, with a median duration of response of 6.3 months versus 4.6 months. The trial will continue as a phase III study. A phase III study of 565 patients compared gemcitabine with the combination of gemcitabine plus the multitargeted antifolate pemetrexed (Alimta) and demonstrated a significant response benefit with the combination (14.8% vs 7.1%; \( P = .004 \)). However, overall and progression-free survival rates were comparable. There was increased hematologic toxicity with the combination. In a phase III trial, 607 patients with metastatic pancreatic cancer were given gemcitabine and erlotinib with either bevacizumab or placebo. Patients receiving bevacizumab had significantly longer progression-free survival, but their improvement in overall survival was not significant (Van Cutsem E, et al: J Clin Oncol 27:2231–2237, 2009). In the CONKO 003 trial, 168 patients who progressed after gemcitabine therapy received 5-FU and leucovorin with or without oxaliplatin. The study demonstrated a significant advantage in progression-free survival favoring patients receiving oxaliplatin (Pelzer U et al: J Clin Oncol 26[15S]: abstract 4508, 2008).

Agents with marginal activity include mitomycin, doxorubicin, ifosfamide, streptozocin (Zanosar), and docetaxel (Taxotere). To date, monoclonal antibody therapy and hormonal manipulation have been ineffective.

**Novel approaches** A progressively better understanding of the molecular biology of pancreatic cancer has revealed numerous new therapeutic targets. Some agents currently being studied include vaccines and dasatinib (Sprycel), an inhibitor of multiple tyrosine kinases. In addition, EndoTAG-1, a cationic liposomal paclitaxel agent, has shown early promise when combined with gemcitabine.

**Pancreatic cystic neoplasms**

Pancreatic cystic neoplasms composed of a variety of neoplasms with a wide range of malignant potential. These neoplasms are divided into serous cystadenomas, mucinous cystadenomas, and intraductal papillary mucinous neoplasms (IPMN). The latter two mucinous neoplasms do carry a malignant potential. These cysts typically require differentiation from inflammatory pseudocysts. The correct diagnosis is paramount to institute appropriate therapy. Differentiating these cystic neoplasms from a pseudocyst is often based on a patient’s prior history.
of pancreatitis and risk factors for pancreatitis. Radiographically, the stigmata of pancreatitis such as diffuse calcifications or inflammatory changes surrounding the pancreas may often help in distinguishing pseudocyst from a cystic neoplasm. Distinguishing serous cyst adenomas from mucinous neoplasm (mucinous adenomas or IMPN) is also important as serous cystadenomas do not have any significant malignant potential. Radiographically, serous cystadenomas occasionally have a starburst appearance with a centrally located scar; this scar is present in approximately 30% of the patients when evaluated with a CT scan. Mucinous cystadenomas often typically have multiple cystic areas with intracystic septae and may occasionally have peripheral calcifications. Furthermore, they occur almost exclusively in females. IPMN are associated with a connection to the pancreatic duct either via endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography (MRCP). This distinguishes IPMN from mucinous cystic neoplasms. Further evaluation of cystic neoplasms often includes endoscopic ultrasound with fine needle aspiration. Analysis of cystic fluid can help in obtaining a correct diagnosis. Cyst fluid CEA has been shown to be the most accurate for differentiating mucinous cystic neoplasms. Whereas a high CEA level (ie, greater than 182 ng/ml) is more indicative of a mucinous cystic neoplasm, a very low cystic fluid CEA is more indicative of a serous cystadenoma. Occasionally it requires a combination of tests to help in distinguishing inflammatory pseudocysts from cystic neoplasm. A multidisciplinary approach incorporating gastroenterologists, surgeons, and radiologists is often required.

With regard to treatment, resection is typically indicated for symptomatic cystic neoplasms, most authorities agree that mucinous cystic neoplasms greater than 3 cm should also be considered for resection in the appropriate medically fit patient.

**PANCREATIC ENDOCRINE TUMORS (PETS)**

PETS cover a spectrum of neoplasms. Many, although not all, of these tumors originate from the pancreatic islets of Langerhans. PETS are not rare. Autopsy studies have documented an incidence as high as 1.5%. Most of these lesions are clinically silent. Approximately 20% of patients with Zollinger-Ellison syndrome (ZES) develop the syndrome in the setting of the multiple endocrine neoplasia type 1 (MEN-1) syndrome. MEN-1 is inherited as an autosomal-dominant trait and is characterized by tumors of multiple endocrine organs, including the pituitary, pancreas, and parathyroid. The gene for MEN-1, which has been localized to the long arm of chromosome 11, has been identified and named **MENIN**. The normal islet contains α, β, γ cells and enterochromaffin cells, which primarily secrete glucagon,
insulin, somatostatin, and serotonin, respectively. All of these hormones may be secreted in excess by PETs. Other hormones that may be secreted by these tumors include vasoactive intestinal peptide (VIP), gastrin, pancreatic polypeptide (PP), and calcitonin. The aggressiveness of a PET in terms of its metastatic potential appears to be due to the cell of origin.

Types of tumors

Insulinomas
These are beta-cell tumors of the pancreatic islets that produce insulin. Four-fifths of insulinomas occur as a solitary lesion, and < 10% of these tumors demonstrate malignant potential (in terms of invasiveness or the development of metastases). In patients with the MEN-1 syndrome, insulinomas are multicentric (10% of patients). In addition, a small group of insulinomas are associated with diffuse islet-cell hyperplasia or nesidioblastosis.

Gastrinomas
These tumors are gastrin-secreting tumors associated with the ZES. These tumors can be either sporadic or familial. Sporadic gastrinomas do not have associated endocrinopathies, whereas hereditary gastrinomas occur in patients with MEN-1 syndrome. Patients with the sporadic form of ZES may have single or multiple gastrinomas. This finding contrasts with patients with hereditary MEN-1 PETs, who generally have a more diffuse tumor process within the pancreas. It is known that 80% to 90% of gastrinomas are located within the “gastrinoma triangle,” defined as the junction of (1) the cystic and common duct, (2) the second and third portions of the duodenum, and (3) the neck and body of the pancreas. Although tumors most characteristiclly are located within the pancreas, a significant percentage of patients with ZES demonstrate primary tumors of the duodenal wall. Extrapancreatic and extraintestinal locations occur in approximately 10% of patients.

More than 90% of gastrinomas are malignant. The spectrum of clinical disease progression includes localized tumors, regional lymph node metastases, and widespread metastatic disease.

Other types
Approximately three-quarters of VIPomas and approximately half of all glucagonomas and somatostatinomas are malignant.

Nonfunctional tumors
Although many PETs cause considerable morbidity due to the inappropriately elevated levels of the hormones that they secrete, even “nonfunctional” PETs, such as those without an associated demonstrable hormone-related syndrome (ie, as PPomas, neurotensinomas, and nonsecretory PETs), may be aggressive. Nonfunctional tumors account for up to 30% of all PETs. Two-thirds of these nonfunctional tumors will demonstrate metastatic lesions at some point during the patient’s lifetime.

Signs and symptoms
The symptom complex that is observed depends on which hormone or hormones are secreted in excess.

Insulinomas
These are associated with symptoms of recurrent hypoglycemia. Diagnosis of these tumors is made by the demonstration of inappropriately elevated levels of insulin, proinsulin, and C peptide at the time of hypoglycemia and an elevated insulin-glucose ratio (> 0.3).

Gastrinomas
Symptoms of gastrinoma-ZES are due to the effect of elevated levels of circulating gastrin. Ulceration of the upper GI tract is seen in > 90% of patients. Diarrhea is the second most common symptom. Approximately 25% of gastrinomas occur in the context of MEN-1 and are associated with parathyroid hyperplasia and hypercalcemia.

The diagnosis of ZES is established by the demonstration of hypergastrinemia (fasting serum gastrin concentration > 1,000 pg/mL) and gastric acid hypersecretion in a patient with ulcerative disease.

VIPomas
An excess of VIP causes a profuse, watery diarrhea, hypokalemia, hypophosphatemia, and hypochlorhydria, referred to as WDHA syndrome.

Glucagonomas
These tumors are associated with a rash (described as a necrotizing migratory erythema), glossitis, cheilosis, constipation and ileus, venous thrombosis, and hyperglycemia. Not all of these manifestations are secondary to elevated glucagon levels alone. The etiology of these signs and
symptoms remains unknown, but some patients respond to supplemental zinc and amino acid infusions.

**Somatostatinomas**
These tumors are rare and are associated with elevated blood glucose levels, achlorhydria, cholelithiasis, and diarrhea.

**Tumor localization**

**Insulinomas**
Ultrasonography, CT, MRI, and selective arteriography with portal vein sampling have been utilized for the preoperative localization of insulinomas. The sensitivity of these preoperative imaging tests ranges from approximately 30% to 60%. This is because 40% of insulinomas measure ≤1 cm and two-thirds of these tumors are < 1.5 cm in size.

Because the success of preoperative localization tests is disappointing, and 90% of these tumors will be found and successfully resected by an experienced endocrine surgeon, there is a general trend toward performing fewer tests. Some centers utilize preoperative ultrasonography if the patient has not undergone prior pancreatic surgery. Other centers still routinely employ portal vein catheterization and angiography. Most centers with EUS availability use the modality as a standard diagnostic tool for these tumors.

More recently, intraoperative sonography has been shown to aid the surgeon. In one series, 84% of tumors not localized preoperatively were correctly located by surgical exploration and intraoperative sonography. Many lesions not discovered by surgical palpation may be found by this technique. At present, there is much less reliance on blind distal resection than was previously advocated. Obviously, the technique of intraoperative ultrasonography may not be as helpful in the MEN-1 syndrome, in which multiple small insulinomas may be found.

**Gastrinomas**
CT, ultrasonography, selective abdominal angiography, selective venous sampling of gastrin, intraoperative ultrasonography, EUS, and intraoperative endoscopy have all been reported to be useful in localizing gastrinomas. More recently, somatostatin receptor scintigraphy (SRS) has become a valuable tool for PET localization; several studies have suggested greater sensitivity and specificity with SRS than with other diagnostic tests.

**Treatment**

**Surgery for insulinomas**
For larger insulinomas in the body or tail of the pancreas, a distal pancreatectomy may be preferable to enucleation. For tumors in the head of the pancreas, enucleation of the tumor is usually possible. Patients with MEN-1 or islet-cell hyperplasia may benefit from an 80% distal pancreatectomy. If the insulinoma is not found at surgery, a blind pancreatectomy is not warranted. Further imaging and venous sampling studies may reveal the exact location of the tumor.
A surgical cure results in normal values on subsequent provocative testing, during which blood insulin and glucose concentrations are measured simultaneously. Some insulinoma recurrences actually represent persistent disease after incomplete tumor excisions or overlooked secondary multiple tumors.

**Surgery for gastrinoma-ZES**
The ideal treatment of gastrinoma-ZES is surgical excision of the gastrinoma. However, this approach is possible in only 20% of patients, most of whom have a sporadic tumor. With the development of effective antisecretory agents and preoperative localization with octreotide scanning, the majority of patients demonstrating widespread metastatic disease can be identified and spared surgical exploration. In addition, some series report that patients with nonmetastatic sporadic gastrinoma may have a higher incidence of extrapancreatic sites than was previously thought. One series has reported that two-thirds of gastrinomas are extrapancreatic.

**Patients with sporadic gastrinoma**
All patients with sporadic gastrinoma should undergo localization studies and be considered for exploratory laparotomy, with the goal of potential cure of ZES. Recent evidence suggests that resection of primary gastrinoma decreases the incidence of liver metastases and ZES. Overall, surgery produces complete remission in approximately 60% of patients with sporadic ZES, and subsequent survival is excellent.

**Patients with ZES and MEN-1**
Some experts believe that surgery should not be used in the management of patients with MEN-1
and ZES. Instead, they recommend treatment with antisecretory medications. This approach is somewhat controversial, as some authors believe that all patients without demonstrated liver metastases should undergo surgery to remove duodenal and pancreatic gastrinomas. Moreover, since many patients with ZES and MEN-1 die of metastatic gastrinoma at a young age, a surgical approach may be warranted. Surgery should be performed only if imaging studies localize the tumor. Although radical surgery may not provide a cure, removal of large tumors may decrease metastatic potential and increase survival.

**Surgical procedure**

During surgery, the entire pancreas should be mobilized and scanned ultrasonographically to permit a thorough examination of the pancreatic head, duodenum, stomach, mesentery, liver, and splenic hilum. Intraoperative endoscopy with transillumination of the bowel wall may also be useful in identifying duodenal lesions. In general, enucleation is the treatment of choice, except for lesions within the duodenal wall, which may require pancreaticoduodenectomy. If no tumor is found, blind distal pancreatectomy should be avoided, since 90% of gastrinomas are located within the gastrinoma triangle. (This triangle is formed by the angles at the junction between the cystic and common bile ducts, the junction between the second and third parts of the duodenum, and the junction between the head and neck of the pancreas.) Surgical resection of liver metastases is controversial. However, several authors have demonstrated meaningful survival in patients with small, isolated lesions. The use of ablative procedures, with open, laparoscopic, or percutaneous techniques, can reduce the neurohormonal tumor burden.

**Radiation therapy for PETs**

**Adjuvant therapy**

The role of adjuvant radiation therapy for PETs of the pancreas is unclear. Because of the rarity of these lesions and their often indolent behavior, the role of this therapy will probably never be demonstrated. However, postoperative irradiation can be considered for patients with positive nodes or microscopically close margins. Concurrent chemotherapy with such agents as 5-FU and/or streptozocin also can be considered. Radiation doses are the same as those used in adjuvant treatment of pancreatic cancer.

**Palliative therapy**

Anecdotal reports indicate that pancreatic PETs may respond to palliative doses of irradiation. Long-term control of unresectable disease has been reported.

**Chemotherapy for PETs**

PETs are more sensitive to chemotherapy than are carcinoid tumors.

**Single agents**

Agents that have demonstrated antitumor activity include recombinant human interferon alfa-2a and alfa-2b (Roferon-A, Intron A, respectively), 5-FU, doxorubicin, dacarbazine, and streptozocin.

**Combination regimens**

Combination chemotherapy is often more effective than is monotherapy. For example, in an ECOG study involving the treatment of patients with PETs, the combination of 5-FU and streptozocin demonstrated a higher response rate than did use of streptozocin alone (63% vs 36%), as well as a better complete response rate (33% vs 12%) and median survival duration (26.0 vs 16.5 months). Therapy with doxorubicin plus streptozocin was superior to therapy with both 5-FU plus streptozocin and single-agent chlorozotocin in terms of response and survival and is the combination most widely used in the United States. Etoposide combined with cisplatin is active in poorly differentiated neuroendocrine malignancies but is marginally effective in well-differentiated lesions.

**New agents**

Antiangiogenic approaches and the recognition of other potential biologic targets have contributed to the development of a number of early-phase clinical trials incorporating bevacizumab with temozolomide (Temodar) and with 5-FU, leucovorin, and oxaliplatin (FOLFOX) chemotherapy, temozolomide with capecitabine, sunitinib (Sutent), sorafenib ( Nexavar), vatalanib, imatinib (Gleevec), thalidomide (Thalomid), temsirolimus (Torisel), and everolimus (Afinitor). Phase III trials are evaluating sunitinib and everolimus. A study of sunitinib versus best supportive care recently was stopped early because of improved results noted for patients receiving the drug.

**Treatment of symptoms**

**Octreotide**

Octreotide (Sandostatin) is often successful in palliating the symptoms of patients with PETs, although this success depends somewhat on the cell type. For example, insulinomas are marginally responsive to octreotide, but gastrinomas and VIPomas often respond. However, when compared
with carcinoid tumors, the median duration of response of PETs to octreotide is significantly shorter (~10 weeks).

SEER data between 1973 and 1999 suggest an increasing median survival of patients with metastatic carcinoid tumors since the era of octreotide treatment. As discussed more fully in the section on carcinoid tumors below, a promising experimental approach for patients whose tumors express somatostatin receptors is the use of octreotide conjugated to a therapeutic radioisotope.

Other agents

Omeprazole (Prilosec), an inhibitor of the function of the parietal cell hydrogen pump, is more effective than histamine type 2 (H₂) -receptor antagonists in blocking gastric acid production and is useful in the symptomatic management of gastrinomas.

Other agents available for symptomatic treatment of insulinomas include diazoxide (Hyperstat), an insulin-release inhibitor, and, more recently, glucagon delivered by continuous infusion through a portable pump. Both of these agents are used in conjunction with frequent high-carbohydrate meals. Patients with the glucagonoma syndrome are treated symptomatically with insulin, high-protein meals, supplemental zinc, amino acid infusions, and anticoagulants.

Hepatic arterial embolization

Hepatic arterial embolization, given with chemotherapy (chemoembolization) or without, is an alternative palliative therapy for patients with either carcinoid tumors or a PET who have predominant liver metastases or symptoms. Embolization is best reserved for patients with < 75% tumor involvement of the liver, bilirubin level < 2 mg/dL, and an ECOG performance status of ≤2. In addition, a patent portal vein is required for this procedure. Other liver-directed therapeutic strategies include radiofrequency ablation (RFA) for select patients and clinical trials investigating the role of yttrium-90 microspheres.

CARCINOID TUMORS OF THE GI TRACT

Carcinoid tumors typically arise from components derived from the primitive gut, lungs, and, rarely, the gonads. Approximately 85% of all carcinoids originate from the gut, predominantly the appendix, followed by the small bowel and rectum. These tumors have the propensity to cause considerable morbidity by virtue of creating a syndrome of hormonal excess. For example, although the majority of carcinoids are hormonally inert, these neoplasms may produce excessive amounts of serotonin (from dietary tryptophan), prostaglandins, kinins (secondary to kallikrein release), and a variety of other hormones, which may account for the “carcinoid syndrome.” SEER data suggest an increase in the incidence of carcinoid tumors between 1973 and 1990.

Signs and symptoms

Flushing

The most common sign of the carcinoid syndrome is flushing, which is often triggered by alcohol, catecholamines, or emotional stress. It ranges in severity from a minor annoyance to profound vasodilatation with near syncope and hypotension.

Diarrhea

Diarrhea is also common and is due to GI hypermotility. It usually occurs after meals and is rarely voluminous, bulky, or foul-smelling.

Abdominal cramps

Diarrhea may be associated with crampy pain, although other etiologies for the pain must be considered, including bowel obstruction due to tumor or mesenteric fibrosis.

Bronchospasm

Patients may also develop bronchospasm, which may be mediated by histamine. This problem is often associated with flushing, although it is less common.

Valvular heart disease

A late finding is right-sided valvular heart disease, although left-sided lesions may be noted occasionally. The fibrous deposits may lead to tricuspid insufficiency and/or pulmonary stenosis. Valve replacement is rarely necessary, however.

Symptom triad

If there is sufficient shunting of dietary tryptophan from niacin to serotonin synthesis, patients may develop diarrhea, dermatitis, and dementia. However, this symptom triad is rare if patients maintain
adequate intake of a balanced diet.

**Diagnosis**

Diagnostic studies include CT/MRI of the abdomen and a 24-hour urine test for 5-hydroxyindoleacetic acid. Some radiologists prefer to obtain a triple-phase CT scan of the liver to detect these highly vascular liver metastases.

**Octreotide scanning**

$^{111}$Indium octreotide scintigraphy (OctreoScan) has a higher sensitivity for detecting pancreatic tumors and is superior to CT or MRI for detecting metastatic disease, particularly extrahepatic disease. One study suggests that $^{111}$indium octreotide scintigraphy can reduce costs by avoiding unnecessary surgeries. Also, a positive scan may predict which patients may benefit from treatment with somatostatin analogs (eg, octreotide). Initial studies with a new peptide tracer, $^{111}$indium 1,4,7,10-tetraazacyclododecane-N,N,N',N'-tetraacetic acid-lanreotide, suggest high tumor uptake and a more favorable dosimetry than is seen with $^{111}$indium diethylene triamine pentaacetic acid-d-Phel-octreotide.

**Prognosis**

**Site and size of tumor**

The site of tumor origin is potentially prognostic, as most appendiceal carcinoids (75%) are < 1 cm when found and are usually cured by resection. Similarly, rectal carcinoids are usually small and completely resectable for cure.

In contrast, small bowel carcinoids tend to present at a more advanced stage, and approximately one third have multicentric primary lesions. However, if the disease is completely resectable, patients have a 20-year survival rate of 80%; patients with unresectable intra-abdominal or hepatic metastases have median survival durations of 5 and 3 years, respectively.

**Treatment**

The management of carcinoid tumors focuses not only on treating bulky disease, as with other solid malignancies, but also on treating the complications of hormonal excess.

**Treatment of bulky disease**

**Surgery**

Appendiceal carcinoids For tumors that are found incidentally in the appendix and that are probably between 1 and 2 cm, appendectomy is the treatment of choice. For tumors > 2 cm, a right hemicolectomy and lymph node dissection are appropriate. The PROMID Study Group recently reported data in a prospective, randomized trial of patients with well differentiated midgut carcinoid. Eighty-five treatment-nave patients were randomized to 30 mg/month of long-acting octreotide or placebo. Treatment was given for 18 months or until tumor progression or death. The median time to tumor progression was significantly longer in the treatment arm (14.3 months) than in the placebo group (6.6 months; $P < .000072$). More than two thirds of patients using octreotide and one third of those given placebo had stable disease. Median overall survival has not been reached in the octreotide arm (Arnold R, et al. *J Clin Oncol* 27[15S]:abstract 4508, 2009).

Small intestines and rectal carcinoids should be resected with a wedge lymph-adenectomy to evaluate nodal disease. Small distal rectal tumors (< 2 cm) can undergo local excision via transanal techniques. Duodenal lesions should be locally excised if they are small (< 2 cm), with radical resection reserved for larger tumors.

**Tumor debulking**

Liver resection or ablation of liver metastases with cryotherapy or radiofrequency techniques is useful in patients with limited extrahepatic disease and/or symptomatic carcinoid syndrome. Tumor debulking can protect liver functional reserve and improve quality of life.

**Liver transplantation** may be of benefit in selected patients without extrahepatic disease whose cancer progresses after other therapeutic interventions.

**Radiation**

Carcinoid tumors are responsive to radiation therapy and frequently are well palliated with this modality. Overall, treatment with higher radiation doses (29–52 Gy) has been associated with higher response rates (40%–50%) than has treatment with lower doses (10%).

**Chemotherapy**

Since carcinoid tumors tend to be resistant to most chemotherapeutic agents, there are no standard
regimens for the treatment of unresectable tumors.

**Single agents** Agents that have reported activity include 5-FU, doxorubicin, and recombinant human interferon alfa-2a and alfa-2b. However, the response rate with these agents is in the range of 10% to 20%, the response duration is < 6 months, and complete remission is rare.

**Combination regimens** Combination chemotherapy regimens represent little improvement over single-agent therapy, with response rates ranging from 25% to 35%, response durations < 9 months, and rare complete remissions.

**New agents** Antiangiogenic approaches and the recognition of other potential biologic targets have contributed to the development of a number of early-phase clinical trials incorporating bevacizumab with temozolomide and with FOLFOX chemotherapy, temozolomide and capecitabine, sunitinib, sorafenib, vatalanib, imatinib, thalidomide, temsirolimus, and everolimus. Phase III trials are planned or ongoing to further evaluate sunitinib and everolimus. The SWOG is currently coordinating an Intergroup randomized phase III trial comparing depot octreotide (Sandostatin LAR) plus interferon alfa-2b versus depot octreotide plus bevacizumab in advanced, poor-prognosis carcinoid patients.

**Treatment of symptoms**

**Somatostatin analogs**

**Octreotide** The most active agent is the somatostatin analog octreotide. Even though native somatostatin is effective in controlling many symptoms, due to its short half-life (< 2 minutes), this agent would have to be administered via continuous infusion to be clinically useful. However, octreotide may be administered subcutaneously every 8 to 12 hours, facilitating outpatient therapy. The initial dose of octreotide is 100 to 600 µg/d in two to four divided doses, although the effective dose varies between patients and must be titrated to the individual patient’s symptoms. Octreotide not only is useful in managing the chronic problems of the carcinoid syndrome, but it also is effective in treating carcinoid crisis (volume-resistant hypotension), which may be precipitated by surgery or effective antitumor treatment.

Octreotide is well tolerated, although chronic treatment may be associated with cholelithiasis, increased fecal fat excretion, fluid retention, nausea, and glucose intolerance. Occasional objective antitumor responses have been observed in patients who have received octreotide; the median duration of symptomatic improvement is 1 year. One report evaluating the cost-effectiveness of octreotide suggested that it may double survival time. Other somatostatin analogs, including lanreotide and vapreotide, are under investigation. A sustained-release formulation of lanreotide (Somatuline Depot) is specifically indicated for the long-term treatment of acromegalic patients who have responded inadequately to surgery and/or radiotherapy or for whom surgery and/or radiotherapy is not an option.

**Depot octreotide** This long-acting somatostatin analog allows for monthly dosing, avoiding the need for daily injections. This relatively new agent improves quality of life while apparently maintaining the same activity seen with daily octreotide. The usual monthly dose is 20 or 30 mg. Patients who demonstrate disease resistance with somatostatin analog treatment alone may benefit from combination therapy with interferon-alpha and this somatostatin analog.

**Radiolabeled somatostatin analogs** A promising experimental treatment approach involves the use of octreotide or other somatostatin analogs conjugated to radioisotopes (eg, 111indium or 90yttrium) in patients whose tumors express somatostatin receptors (eg, those with a positive OctreoScan result). This approach allows targeted in situ radiotherapy by taking advantage of internalization of the radioligand into the cell to produce DNA damage and cell death, with little effect on normal tissue. Initial reports have shown favorable results with this technique.

**Other agents**

Other agents that have been used for symptomatic management include histamine type 1 (H1)- and H2-receptor antagonists, methoxamine (Vasoxyl), cyproheptadine, and diphenoxylate with atropine. The symptom complex of diarrhea, dermatitis, and dementia may be prevented or treated with supplemental niacin. A retrospective analysis of 177 patients with adrenocortical cancer who had undergone radical surgery has reported the recurrence-free survival for individuals who received adjuvant mitotane (47 patients) compared with those who did not (130 patients total from two different control groups). Mitotane had a significant advantage for recurrence-free survival (42 months vs 10 and 25 months in the two control groups; hazard ratio: 2.91 and 1.97) (Terzolo M, et al: N Engl J Med 356:2372–2380, 2007).

**Hepatic arterial embolization**

Hepatic arterial embolization with such agents as Ivalon or Gelfoam, with or without chemotherapy (chemoembolization), is an option for patients with either a carcinoid tumor or an islet-cell carcinoma.
who have predominant liver metastases or who are symptomatic. These lesions often are hypervascular, and, thus, peripheral hepatic embolization may provide symptomatic relief in some patients. It is unclear whether this therapy has any effect on patient survival.

Other liver-directed therapeutic strategies include RFA for select patients and, as is being investigated in clinical trials, the possible use of 90yttrium microspheres.

**ADRENOCORTICAL CARCINOMA**

Adrenocortical carcinoma is a rare, highly malignant neoplasm that accounts for about 0.2% of cancer deaths. Long-term survival is dismal overall; the survival rate is 23% at 5 years and 10% at 10 years.

**Etiology**

The etiology of adrenocortical cancer is unknown, but some cases have occurred in families with a hereditary cancer syndrome.

**Signs and symptoms**

Approximately half of adrenocortical neoplasms produce hormonal and metabolic syndromes of hormone hypersecretion (such as Cushing’s syndrome, virilizing or feminizing syndromes, and hyperaldosteronism). In children, Cushing’s syndrome is rare but is often due to adrenal carcinoma. Mixed syndromes, such as Cushing’s syndrome and virilization, strongly suggest adrenal carcinoma. The combination of hirsutism, acne, amenorrhea, and rapidly progressing Cushing’s syndrome in a young female is a typical presentation. In men, estrogen-secreting tumors are associated with gynecomastia, breast tenderness, testicular atrophy, impotence, and decreased libido. Often, the diagnosis of adrenocortical carcinoma is not evident until the discovery of metastases or until the primary tumor becomes large enough to produce abdominal symptoms. Smaller tumors may be discovered incidentally, when unrelated abdominal complaints are investigated radiographically.

**Treatment**

**Surgery**

Complete surgical resection is the treatment of choice in patients with localized disease, as it offers the best chance of extending the disease-free interval and survival.

**Medical therapy**

**Mitotane (Lysodren)**

This drug is one of only a few effective agents; it exerts a specific cytolytic effect on adrenocortical cells and has been used to treat unresectable or metastatic adrenocortical carcinoma. Only 15% to 30% of patients experience objective tumor regression, with a median duration of about 7 months. Mitotane is given at a dose of 4 to 8 g/day as tolerated, although the dose is variable.

**Chemotherapy**

Doxorubicin has been of benefit in a limited number of patients, and combination chemotherapy is under investigation.

Suramin, a sulfonated drug that is cytotoxic to human adrenocortical carcinoma cell lines, has been evaluated but has not proven useful in inoperable adrenocortical cancer. Innovative chemotherapy programs are clearly needed for this disease.

**Controlling hormone hypersecretion**

Hormone hypersecretion can be controlled medically, in most cases. Agents that are effective in reducing steroid production and in palliating associated clinical syndromes include the anti-fungal drug ketoconazole, 800 mg/day; aminoglutethimide (Cytadren), 1 to 2 g/day; and metyrapone (Metopirone), 1 to 4 g/day or higher as needed to control cortisol levels. These agents may be used alone or with mitotane.

**PHEOCHROMOCYTOMA**

Pheochromocytomas are catecholamine-secreting tumors that arise from chromaffin cells in the adrenal medulla or extra-adrenal sympathetic ganglia. These tumors constitute a surgically correctable cause of hypertension in 0.1% to 1.0% of hypertensive persons. Only about 10% of pheochromocytomas are considered to be malignant. The vast majority (90%) of
pheochromocytomas are found in the adrenal medulla, and 97% are located below the diaphragm. Approximately 10% each of pheochromocytomas are bilateral, malignant, multifocal, extra-adrenal, found in children, or associated with a familial syndrome. Pheochromocytomas in patients with familial syndromes, such as MEN-2 and von Hippel-Lindau syndrome, are less likely to be malignant than are other adrenal lesions. In contrast, pheochromocytomas in patients with a family history of malignant pheochromocytoma are more apt to be malignant.

**Epidemiology and etiology**

Pheochromocytomas occur in all age groups, but the incidence peaks in the third to fifth decades of life. Most pheochromocytomas (90%) are sporadic. Approximately 10% of cases are inherited as an autosomal-dominant trait, either independently or as a part of the MEN-2 syndrome; bilateral tumors are more common in this setting.

Both MEN-2A and MEN-2B include medullary thyroid carcinoma and pheochromocytoma. MEN-2A includes hyperparathyroidism, whereas MEN-2B includes ganglioneuromas and marfanoid habitus. In MEN-2 families, pheochromocytoma occurs in 5.5% to 100% (mean, 40%), depending on the kindred studied. Bilateral medullary hyperplasia is almost always present. Pheochromocytomas are bilateral in 70% of cases and usually multicentric, but they are rarely extra-adrenal or malignant.

**Signs and symptoms**

Patients can present with various symptoms, ranging from mild labile hypertension to hypertensive crisis, myocardial infarction, or cerebral vascular accident, all of which can result in sudden death. The classic pattern of paroxysmal hypertension occurs in 30% to 50% of cases; sustained hypertension may also occur and resembles essential hypertension. A characteristic presentation includes “spells” of paroxysmal headaches, pallor or flushing, tremors, apprehension, palpitations, hypertension, and diaphoresis.

**Diagnosis**

The diagnosis of pheochromocytoma relies on an appropriate history and documentation of excessive catecholamine production.

**Catecholamine measurements**

Measurement of 24-hour urinary catecholamines and their metabolites, vanillylmandelic acid and metanephrine, is commonly used; the metanephrine level is considered to be the most specific single test. Serum catecholamine measurements are more susceptible to false elevations due to stress-related physiologic fluctuations. The evaluation of serum catecholamines after clonidine suppression, however, provides a useful diagnostic tool that is more convenient than urine collection. Dynamic provocative tests are rarely indicated. Recently, the measurement of plasma-free metanephrines has been shown to be an excellent test for excluding or confirming pheochromocytoma.

**Radiologic studies**

Almost all pheochromocytomas are localized in the abdomen, mostly in the adrenal medulla; other locations include the posterior mediastinum or any distribution of the sympathetic ganglia. After the diagnosis is established biochemically, radiologic methods may be needed for preoperative localization of the lesion; CT and MRI are most widely used. Iodine methyl-iodobenzyl guanidine (MIBG) and SRS provide a “functional” image; they are most helpful in the detection of occult contralateral or extra-adrenal lesions.

**Differentiating benign from malignant tumors**

The histologic differentiation between benign and malignant lesions is extremely difficult and often impossible to make; this distinction may require the development of lymph node, hepatic, bone, or other distant metastases. Recurrent symptoms of pheochromocytoma, often emerging many years after the original diagnosis, are suggestive of malignancy. Biochemical confirmation of recurrent catecholamine hypersecretion and localization of metastatic lesion(s) with 131iodine-MIBG scan constitute diagnostic proof.

**Treatment**

**Preoperative medical management**

Phenoxybenzamine (Dibenzyline), an oral, long-acting, noncompetitive alpha-adrenoceptor blocker,
is a widely used, very helpful first drug; it is given at a dose of 10–40 mg/day. Propranolol, a beta-blocker (20–80 mg/day), is usually added after a few days to prevent tachycardia or arrhythmia. The use of beta-blockers alone is hazardous, because it may precipitate a paradoxical rise in blood pressure. The tyrosine hydroxylase inhibitor metyrosine (Demser) may be added in patients whose blood pressure is not well controlled with the combination of an alpha- and a beta-blocker.

Surgery
The principles of pheochromocytoma resection are complete tumor resection, avoidance of tumor seeding, and minimal tumor manipulation. Adrenalectomy can be performed by means of an open anterior transabdominal, open posterior retroperitoneal, laparoscopic lateral transabdominal, or laparoscopic posterior retroperitoneal approach. In the past, an open anterior approach was the standard, because it allowed for complete exploration and inspection for potential tumor foci. However, with the improved accuracy of preoperative imaging and increased experience with laparoscopic procedures, there is little need for exploration in areas in which a tumor has not been identified.

Except in tumors > 6 cm, the laparoscopic approach to pheochromocytoma is probably the technique of choice. In the absence of obvious local tumor invasion or metastatic disease, a laparoscopic procedure is acceptable to many experienced endocrine surgeons. The most critical intraoperative aspect of surgery is control of blood pressure immediately after removal of the tumor, when all agonistic effects are abolished and the effects of alpha- and beta-blockers are still present. Close cooperation with the anesthesiologist to expand fluid volume and prepare the appropriate infusions of agonists to support vascular stability is critical.

Treatment of metastatic malignant pheochromocytoma
The treatment of choice for metastatic malignant pheochromocytoma remains problematic.

Medical and radiation therapy
Medical therapy with alpha- or beta-blockers, as well as metyrosine, is almost always required to maintain hemodynamic stability. Chemotherapy utilizing streptozocin-based regimens or the combination of cyclophosphamide, vincristine, and dacarbazine has yielded promising responses. Treatment with 131Iodine–MIBG or (in Europe) with radiolabeled somatostatin has met with only limited success; however, clinical trials continue to investigate these approaches. In most cases, uncontrolled catecholamine hypersecretion eventually escapes biochemical blockade, and fatal hypertensive crisis ensues.

Surgery
In those cases in which limited and resectable lesions can be identified, surgery can effect complete and lasting remission of the disease.

References:

SUGGESTED READING

ON PANCREATIC CANCER


ON Neuroendocrine GI Tumors


on adrenal neoplasms


ON CARCINOIDS


on PHEOCHROMOCYTOMAS


Abbreviations in this chapter
AJCC = American Joint Committee on Cancer; ACOSOG = American College of Surgeons Oncology Group; CALGB = Cancer and Leukemia Group B; CONKO = Charité Onkologie Clinical Studies in GI Cancer; ECOG = Eastern Cooperative Oncology Group; ESPAC = European Study Group for Pancreatic Cancer; EORTC = European Organisation for Research and Treatment of Cancer; GITSG = Gastrointestinal Tumor Study Group; NCIC = National Cancer Institute of Canada; PROMID = Placebo-controlled Prospective Randomized Study on the Antiproliferative Efficacy of Octreotide LAR in Patients with Metastatic Neuroendocrine Midgut Tumors; RTOG = Radiation Therapy Oncology Group; SEER = Surveillance, Epidemiology and End Results; SWOG = Southwestern Oncology Group

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