Pancreatic, Neuroendocrine GI, and Adrenal Cancers

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- **TABLE OF CONTENTS**

- **Pancreatic Cancer**
- Incidence and Epidemiology
- Etiology and Risk Factors
- Signs and Symptoms
- Screening and Diagnosis
- Pathology
- Staging and Prognosis
- Treatment
- **Pancreatic Cystic Neoplasms**
- **Pancreatic Endocrine Tumors**
- **Carcinoid Tumors of the GI Tract**
- **Adrenocortical Carcinoma**
- **Pheochromocytoma**
- **Suggested Reading**

PANCREATIC CANCER

Pancreatic cancer is the fourth leading cause of cancer death in the United States. In 2012, an estimated 43,920 new cases were diagnosed, and 37,390 deaths occurred.

Incidence and Epidemiology

Gender

The incidence of pancreatic cancer is slightly higher in men than in women. These gender differences are most prominent among younger individuals.

Age

(**MORE:** Colorectal Lesions)

The peak incidence of pancreatic carcinoma occurs in the seventh decade of life. Two-thirds of new cases occur in people > 65 years of age. Recently, several epidemiologic studies have demonstrated worrisome projections regarding pancreatic cancer: An analysis of the Surveillance, Epidemiology and End Results (SEER) database has projected a marked increase in the number of cancer cases in the next 20 years, which is attributed to the increasing number of adults over the age of 65. The authors estimated that there will be a 55% increase in the number of pancreatic cancer cases over the next 20 years.

Race

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

Survival

Cancer of the pancreas is a highly lethal disease, with ductal adenocarcinoma being the most common histologic type. The overall 5-year survival has not improved in the past 30 years and remains < 5%. Median survival is approximately 6 months for patients with metastatic disease and 10 months for patients with locally advanced disease. Of approximately 50% of patients with pancreatic adenocarcinoma who present with clinically apparent metastatic disease, only a minority (10%-20%) of patients are considered resectable. There have been some increases in 5-year survival following a curative resection (21%-25%), potentially due to increased referral to higher-volume teaching institutions; however, 50% of patients die of recurrent tumor within 2 years.

In the past, surgical resection has been associated with high morbidity and mortality. In the last 20 years, however, there have been marked improvements in outcomes following resection. Several single-institution series have reported mortality rates of < 3% following resection. Factors that appear to be important in predicting long-term survival following resection include clear surgical margins, small tumor size (< 2 cm), negative lymph nodes, and reduced perioperative morbidity.
Back to Top

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 pancreatic malignancies. Heavy cigarette smokers have at least a twofold greater risk for 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. However, no study has directly linked dietary carcinogens to pancreatic cancers in humans. A recent report evaluated the association between dietary nitrate and nitrite intake and pancreatic cancer risk in the National Institute of Health (NIH)-AARP Diet and Health Study. This study showed modest evidence that processed meat sources of dietary nitrate and nitrite may be associated with pancreatic cancer among men only.

Caffeine

The contribution of caffeine(Drug information on caffeine) consumption to the development of pancreatic carcinoma is controversial. One case-controlled study showed a correlation between caffeine consumption and pancreatic cancer. However, most other studies including a meta-analysis have been equivocal.

Alcohol

There has been no clear-cut relationship shown between alcohol(Drug information on alcohol) use and pancreatic carcinoma.

Diabetes

Hyperglycemia does not seem to be a risk factor for pancreatic cancer. However, 10% of all patients are found to have new-onset diabetes mellitus with the diagnosis of pancreatic carcinoma.

Obesity

A report by the American Institute for Cancer Research (AICR) and the World Cancer Research Fund (WCRF) estimated that 28% of pancreatic cancers can be attributable to obesity. As the obesity problem in the United States worsens, this percentage may continue to increase *(WCRF/AICR report, Policy and Action for Cancer Prevention, 2009)*.

Genetic factors

More than 80% of resected pancreatic cancers have been found to harbor activating point mutations in the oncogene *KRAS*. In addition, the tumor-suppressor genes *pl6*, *CDKN2A*, *TP53*, *SMAD4*, and *DPC4* are 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.
Cancer of the pancreas may be a genetic disease. 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. There are currently no genetic tests or screening recommendations for families with suspected hereditary pancreatic syndromes.
Back to Top

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 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 elderly patients should alert physicians to the possibility of pancreatic carcinoma.

Palpable gallbladder

When it occurs without cholecystitis or cholangitis, a palpable gallbladder suggests malignant obstruction of the common bile duct until proved otherwise. This so-called Courvoisier's sign is present in about 25% of patients with pancreatic cancer.
Other physical findings. 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).

- **TABLE OF CONTENTS**
- **Pancreatic Cancer**
- Incidence and Epidemiology
- Etiology and Risk Factors
- Signs and Symptoms
- Screening and Diagnosis
- Pathology
- Staging and Prognosis
- Treatment
- **Pancreatic Cystic Neoplasms**
- **Pancreatic Endocrine Tumors**
- **Carcinoid Tumors of the GI Tract**
- **Adrenocortical Carcinoma**
- **Pheochromocytoma**
- **Suggested Reading**

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 biliary obstruction or jaundice, because 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.

Laparoscopy

This diagnostic tool is useful for staging patients with pancreatic carcinoma and for formulating treatment plans. Approximately 10% to 15% of patients considered 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.

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 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 about 70%.
CT. This diagnostic tool provides better definition of the tumor and surrounding structures than does ultrasonography. CT scan is also 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 (with thin "cuts" of the pancreas) increases the accuracy of detecting pancreatic carcinoma in general and vessel encasement in particular. This technique permits rapid data acquisition and computer-generated 3D images of the mesenteric arterial and venous tributaries on many planes. Spiral CT is quicker and less expensive than angiography and uses less contrast medium.
PET. The use of positron emission tomography (PET) with ^{18}fluorodeoxyglucose (FDG) in the evaluation of patients with pancreatic cancer has been proposed for evaluation of the primary tumor and detection of distant metastases. A 2001 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%). Although potentially useful in selected clinical scenarios, routine application of FDG-PET for pancreatic cancer staging is not recommended by consensus groups, including the National Comprehensive Cancer Network (NCCN).
MRI. MRI is considered equivalent to pancreatic protocol CT imaging for the initial evaluation of pancreatic cancer by consensus groups, including the NCCN. Although MRI techniques have improved, endoscopic retrograde cholangiopancreatography (ERCP) is mandatory for the workup of many patients, in particular those who require therapeutic intervention such as stent placement.
Endoscopic ultrasonography (EUS). 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. EUS is also valuable in obtaining tissue confirmation of the pancreatic mass before starting treatment for unresectable or borderline resectable lesions.
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 (pancreatic intraepithelial neoplasia).
Endoscopic retrograde cholangiopancreatography (ERCP). This technique may some day be supplanted as a diagnostic tool by EUS and magnetic resonance cholangiopancreatography (MRCP), although ERCP is now 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. Complications of bile and pancreatic duct manipulation include infection and pancreatitis. These risks must be carefully weighed against the added value of ERCP in a completely imaged patient.
Back to Top

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

TABLE 1 TNM staging of pancreatic tumors

FIGURE 1 Actuarial survival as a function of regional lymph node status in patients with pancreatic cancer.

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.
Back to Top

Staging and Prognosis

Pancreatic adenocarcinoma is staged according to local spread of disease, nodal status, and distant metastatic involvement using the American Joint Committee on Cancer (AJCC) TNM system (**Table 1**). The tumor (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 values 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

Prior to the era 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.

- **TABLE OF CONTENTS**
- **Pancreatic Cancer**
- Incidence and Epidemiology
- Etiology and Risk Factors
- Signs and Symptoms
- Screening and Diagnosis
- Pathology
- Staging and Prognosis
- Treatment
- Surgical treatment of resectable disease
- Surgical palliation
- Neoadjuvant and adjuvant therapies
- Treatment of unresectable lesions
- Treatment of metastatic adenocarcinoma
- **Pancreatic Cystic Neoplasms**
- **Pancreatic Endocrine Tumors**
- **Carcinoid Tumors of the GI Tract**
- **Adrenocortical Carcinoma**
- **Pheochromocytoma**
- **Suggested Reading**

Treatment

Surgical treatment of resectable disease

The rate of resection for curative intent ranges from 10% to more than 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 surgeons who treat 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.

Currently, pancreatic lesions may be classified as resectable, borderline resectable, and unresectable. The definiton of borderline resectable tumors includes impingement or abutment on the SMV/portal 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.

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, although EUS is not as reliable as the other modalities for assessing vascular involvement. 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.

Operative intervention.

• *Intraoperative biopsy*—Most patients with resectable pancreatic 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. In patients without a histologic diagnosis, however, a biopsy is warranted in patients considered unresectable who are undergoing an attempt at resection.

• *Whipple vs pylorus-preserving procedure*—If the tumor is deemed to be resectable, a standard pancreaticoduodenectomy (Whipple procedure) or pylorus-preserving Whipple (PPW) procedure is performed. The PPW option theoretically eliminates the nutritional problems caused by a reduced gastric reservoir and gastric dumping, but 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 recommended. Recent prospective randomized studies have shown therthat there is no significant difference in clinical or oncologic outcomes between pylorus-preserving and standard Whipple resection.

• *Reconstruction technique*—The most common reconstruction technique after a Whipple resection utilizes the proximal jejunum in an ante or retrocolic position to complete the pancreaticojejunostomy, which is followed by a hepaticojejunostomy and gastrojejunostomy. Pancreaticogastrostomy is also an effective and safe means of creating the anastomosis.

• *Postoperative complications*—Analysis of national databases indicate that the average post-operative mortality rate following pancreaticoduodenectomy is 6% to 8%, however studies from high-volume centers report a mortality rate of < 2%.

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 < 5% for those with positive nodes. 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%, vs 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 on presentation. For patients who are surgical candidates, resection employs a distal pancreatectomy with concomitant splenectomy. Because of the large size of these tumors, 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.

Back to Top

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. Nonoperative means of biliary decompression can often be accomplished with endoscopically placed expandable metallic stents. The use of metal stents should be reserved for patients who have been fully evaluated and deemed unresectable by a multidisciplinary team.

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 alcohol injection of the celiac plexus, 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 assuage tumor pain. (For further discussion of these techniques, see the "Pain Management" chapter.)

Back to Top

Neoadjuvant and adjuvant therapies

Radiation therapy.

• *Preoperative chemoradiation therapy*—Several single-institution studies have evaluated the role of preoperative irradiation in conjunction withfluorouracil(Drug information on fluorouracil) (5-FU)- and gemcitabine(Drug information on gemcitabine)-based chemotherapy. In these studies, 60% to 80% of the lesions were completely resected 1 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 vs postoperative sequencing.

The appropriate radiation dose and volume are dependent on the planned concurrent chemotherapy. For patients undergoing concurrent 5-FU–based neoadjuvant chemoradiation, doses of 4,500 to 5,000 cGy are appropriate with inclusion of both the primary tumor and elective nodal coverage. Although interest in concurrent gemcitabine-based approaches was initially tapered by high rates of GI toxicity, treatment with full-dose gemcitabine (eg, 1000 mg/m^2) appears to be well tolerated when radiation treatment volumes are limited to the primary tumor and omit elective nodal coverage. There are research initiatives to further address the role of neoadjuvant chemotherapy. For example, the recent data demonstrating the high response rate from the FOLFIRINOX regimen (5-FU, leucovorin, irinotecan(Drug information on irinotecan), and oxaliplatin(Drug information on oxaliplatin)) in metastatic pancreatic cancer are of interest to determine if this combination will enhance resectability when used in the neoadjuvant setting, and are the subject of a new NCI GI Intergroup study of FOLFIRINOX followed by chemoradiation and surgery.

A randomized phase III trial including 342 patients (Conroy T et al: *N Engl J Med* 2011) compared the combination chemotherapy regimen of 5-FU, irinotecan, leucovorin, and oxaliplatin (FOLFIRINOX) to standard gemcitabine, showing significant improvement in response rates (31.8% vs 11.3%, $P < .001$), progression-free survival (6.4 months vs 3.3 months, $P < .001$) and survival (11.1 months vs 6.8 months, $P < .001$). This regimen is best reserved for patients with good performance, given the potential toxicity .

• *Postoperative chemoradiation therapy*—The role of radiotherapy in the adjuvant setting has been called into question by several European trials. Criticism of these studies includes lack of quality control and suboptimal chemotherapy and radiotherapy schedules in the arms that included radiotherapy. In addition, for most GI sites, the preferred sequencing of modalities has been to give several months of full-dose multidrug chemotherapy before proceeding to radiotherapy with concurrent chemotherapy, a sequencing that was not used in the European trials.

A recently activated clinical trial being conducted by the European Organisation for Research and Treatment of Cancer (EORTC), Radiation Therapy Oncology Group (RTOG), and the Southwestern Oncology Group (SWOG) addresses all of these criticisms. Postoperative care for patients with cancer of the pancreatic head will be double-randomized, with all patients receiving six cycles of gemcitabine. The first randomization will be to receive or not receive concurrent erlotinib with gemcitabine. The second randomization will be whether to administer either no further therapy or radiotherapy (50.4 Gy/28 fractions) with concurrent infusional fluorouracil or equivalent capecitabine(Drug information on capecitabine) (Xeloda). All radiotherapy treatment plans will be centrally reviewed in advance of treatment. Thus, this trial is evaluating the contribution of postoperative radiotherapy using standard-of-care techniques with proactive quality control.

The American College of Surgeons Oncology Group (ACOSOG) Z05031 trial was a phase II trial that tested a regimen of radiation therapy, cisplatin(Drug information on 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 Intergroupcompleted a randomized phase II trial to explore new combinations incorporating the monoclonal antibodies bevacizumab(Drug information on bevacizumab)(Avastin) and cetuximab(Drug information on cetuximab) (Erbitux), each given with gemcitabine; irradiation was given with oral capecitabine. Theresults suggest no added benefit with the addition of either bevacizumab or cetuximab.

Postoperative chemotherapy. A German randomized phase III trial including 368 patients with resected pancreatic cancer compared postoperative gemcitabine given for 6 months vs observation. Disease-free survival was significantly greater 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). 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 vs 9% in the observation arm was reported.

The European Study Group for Pancreatic Cancer (ESPAC)-3 was a multicenter randomized phase III trial which compared adjuvant fluorouracil vs gemcitabine following resection of pancreatic cancer. Following R0/R1 resection, patients were randomized to 5-FU (425 mg/m^2) bolus on days 1-5 every 28 days vs gemcitabine (1,000 mg/m^2) given intravenously on days 1, 8, and 15 every 4 weeks. Both regimens were continued for 6 months. A total of 1,088 randomized patients were enrolled after a minimum follow-up of 2 years, median survival for the 5-FU/leucovorin group was 23 months, compared with 23.6 months for the gemcitabine group. There was no statistical difference between the two study arms.

Another report from the ESPAC-3 periampullary adenocarcinoma trial including 428 patients determined that adjuvant chemotherapy (5FU or gemcitabine) vs observation did not show a survival difference in the primary analysis; however, multivariable analysis adjusting for prognostic variables showed a survival benefit favoring adjuvant chemotherapy.

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 trimodal therapy is crucial for margin-free resection and long-term survival. A meta-analysis from the ESPAC-1 trial showed that chemotherapy alone is ineffective for patients who have had resection for microscopic disease at a margin (R1), thus adding further support for both chemotherapy and radiation therapy for these borderline resectable patients. As mentioned, the NCI GI Intergroup is conducting a study of FOLFIRINOX followed by chemoradiation followed by surgery for borderline resectable patients.

Back to Top

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.

Chemoradiation. The addition of chemotherapy to radiation therapy has been shown to improve the survival of patients with unresectable pancreatic adenocarcinoma. In a Gastrointestinal Tumor Study Group (GITSG) trial of unresectable disease conducted in the 1970s, 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). Given the study era, radiotherapy was administered using two dimensional split-course techniques. 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).

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 no significant advantage for chemoradiation followed by chemotherapy compared with chemotherapy alone.

The Eastern Cooperative Oncology Group (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 11.1 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.

Based on these data, many practitioners would favor several months of gemcitabine-based chemotherapy before proceeding to chemoradiotherapy. This allows early delivery of optimal chemotherapy and spares the patient destined to rapid dissemination of disease from the morbidity associated with use of concurrent chemoradiotherapy. If radiotherapy is given concurrently with 5-FU, elective nodal doses of 4,500 cGy and primary tumor doses of 5,400 cGy based on bowel tolerance are appropriate. In all cases, delineation of the target volume should incorporate all available diagnostic imaging. Image-guided radiation therapy (IGRT) is appropriate to ensure patient setup and daily target visualization.

• *Approaches under investigation*—At present, clinical investigators are considering a variety of chemoradiation therapy approaches including the addition of new targeted therapies in early phase trials. The benefit of irradiation for patients with locally advanced disease, however, remains of interest for clinical trials because of toxicity concerns and the relatively brief survival rates.

Objective response by size criteria is difficult to achieve with radiotherapy. This may be due to the substantial sclerotic component associated with pancreatic adenocarcinomas rather than true radiation resistance. Regardless, until it becomes possible to achieve a high incidence of objective clinical

responses, it will be difficult to persuade surgeons to attempt resections after chemoradiotherapy for unequivocal clinical T4 lesions. Recent results reported from the University of Michigan and Rush University Medical Center are of particular interest in this regard. The Michigan group has a long interest in concurrent radiotherapy and gemcitabine because of the drug's radiosensitizing properties. Previous work from the group suggested that normal tissue tolerance limits the ability to give full doses of both radiotherapy and gemcitabine concurrently. However, in their most recent work, these investigators have taken advantage of technical developments in radiation oncology by using IMRT, breath-holding techniques to limit respiratory excursion, and online daily setup verification to treat macroscopic disease with tight planning target volumes. Radiation doses were successfully escalated to 5,500 cGy in 25 fractions over 5 weeks with gemcitabine (1,000 mg/m^2 over 100 minutes) given on weeks 1, 2, 4 and 5. Objective responses were seen in 52% of 27 cases, with a mean overall survival of 23 months, including two cases converted to resectable status with minimal residual disease at surgery.

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/m^2/wk) are given concurrently with irradiation, the volume of radiation must be markedly reduced to avoid unacceptable GI toxicity. In the Michigan series, the treatment volume included the primary tumor only plus a 1-cm planning target volume (PTV) margin, with omission of nodal coverage.

Back to Top

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.

Chemotherapy. Because 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, because their likelihood of deriving any benefit is exceedingly slim. However, patients who desire therapy and who, while symptomatic, still have good performance status may be offered "standard" chemotherapy (**Table 2**), or, if possible, they should be encouraged to participate in a clinical trial.

TABLE 2 Chemotherapy regimens for pancreatic cancer

• *5-FU*—Historically, single-agent 5-FU has been associated with a response rate of up to 25% in pancreatic cancer. The use of 5-FU, doxorubicin(Drug information on doxorubicin), and mitomycin(Drug information on mitomycin) (FAM) and 5-FU plus doxorubicin offer no advantage over 5-FU alone. 5-FU plus leucovorin appears to be ineffective.

• *Gemcitabine*—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 vs 4.8% of the 5-FU–treated group. Due to its palliative potential, gemcitabine has become the standard of care for patients with unresectable, metastatic 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 vs 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 of 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 patients with good performance status (10.1 vs 7.4 months; $P = .014$).

A phase III study of 565 patients compared gemcitabine vs the combination of gemcitabine plus the multitargeted antifolate pemetrexed(Drug information on 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.

Three Intergroup metastatic pancreatic cancer trials have been reported. 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 groups had approximately 1 month longer median survival). Cancer and Leukemia Group B (CALGB) compared bevacizumab plus gemcitabine vs gemcitabine alone, and SWOG evaluated gemcitabine with or without cetuximab. These studies reported no difference in outcome with the addition of an antibody.

In a phase III trial, 607 patients with metastatic pancreatic cancer were given gemcitabine and erlotinib (Tarceva) with either bevacizumab or placebo. The results, published in 2009 by Van Cutsem et al, showed that patients receiving bevacizumab had significantly longer progression-free survival, but their improvement in overall survival was not significant. In the Charité Onkologie Clinical Studies in GI Cancer (CONKO) 003 trial, presented at the 2008 ASCO meeting, 168 patients who progressed after gemcitabine therapy received 5-FU and leucovorin with or without oxaliplatin (Eloxatin). The study demonstrated a significant advantage in progression-free survival favoring patients receiving oxaliplatin.

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; HR = 0.82; *P* = .038) and progression-free survival (HR = 0.77; *P*= .007). As with other epidermal growth factor receptor-targeted agents, rash was associated with response. Diarrhea increased with the combination.

Patients with good performance status who progress after gemcitabine-based therapy may respond to second-line therapies including FOLFOX, FOLFIRI, and capecitabine, as noted in small studies.

• *Agents with marginal activity*—Agents with marginal activity include mitomycin, doxorubicin, ifosfamide(Drug information on ifosfamide), streptozocin (Zanosar), and docetaxel(Drug information on 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, mTOR inhibitors, hedgehog pathway inhibitors, and inhibitors of multiple tyrosine kinases as examples. In addition, Abraxane (nanoparticle paclitaxel(Drug information on paclitaxel)) and EndoTAG-1, a cationic liposomal paclitaxel agent, have shown early promise when combined with gemcitabine, and are currently being tested in a randomized phase III trial.

- **TABLE OF CONTENTS**
- **Pancreatic Cancer**
- **Pancreatic Cystic Neoplasms**
- **Pancreatic Endocrine Tumors**
- **Carcinoid Tumors of the GI Tract**
- **Adrenocortical Carcinoma**
- **Pheochromocytoma**
- **Suggested Reading**

PANCREATIC CYSTIC NEOPLASMS

Pancreatic cystic neoplasms are made up 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 carry a malignant potential. These cysts typically require differentiation from inflammatory pseudocysts. The correct diagnosis is paramount in order 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 cystadenomas from mucinous neoplasms (mucinous adenomas or IPMN) is also important because 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 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 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 carcinoembryonic antigen (CEA) has been shown to be the most accurate for differentiating mucinous cystic neoplasms. Whereas a high CEA level (ie, > 182 ng/mL) is more indicative of a mucinous cystic neoplasm, a very low cystic fluid CEA (< 5 ng/mL) is more indicative of a serous cystadenoma.

Occasionally, it requires a combination of tests to help distinguish 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 and those associated with a solid component or mural nodule. Most authorities agree that mucinous cystic neoplasms greater than 3 cm should also be considered for resection in the appropriate medically fit patient.

- **TABLE OF CONTENTS**
- **Pancreatic Cancer**
- **Pancreatic Cystic Neoplasms**
- **Pancreatic Endocrine Tumors**
- Types of Tumors
- Signs and Symptoms
- Tumor Localization
- Treatment
- **Carcinoid Tumors of the GI Tract**
- **Adrenocortical Carcinoma**
- **Pheochromocytoma**
- **Suggested Reading**

PANCREATIC ENDOCRINE TUMORS

Pancreatic endocrine tumors (PETs) or pancreatic neuroendocrine tumors (PNETs) cover a spectrum of neoplasms. These tumors may produce clinical syndromes based on excessive hormone production (see below), or produce symptoms (abdominal pain, jaundice, etc) by mass effect in tumors that do not secrete hormones (nonfunctional tumors). With the increased use of CT scanning, there are a greater number of identified nonfunctioning neuroendocrine tumors of the pancreas.
PETs are not rare. Autopsy studies have documented an incidence of 1.5%. Most of these lesions are clinically silent.
Approximately 20% of patients with Zollinger-Ellison syndrome (ZES) develop PETs in the setting of multiple endocrine neoplasia type 1 (MEN-1). 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, and γ cells, and enterochromaffin cells, which primarily secrete glucagon(Drug information on glucagon), insulin, somatostatin(Drug information on 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 a factor of the cell of origin.
The natural history of PETs is highly variable. As noted, many remain asymptomatic and undiagnosed. Others, with poorly differentiated histology, may be quite malignant and spread to distant organs. The behavior and treatment of these tumors are similar to small-cell lung cancer.
Back to Top

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). A small group of insulinomas is associated with diffuse islet-cell hyperplasia or nesidioblastosis.

Gastrinomas

These tumors are gastrin-secreting tumors associated with the ZES. They 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 contrasts with the finding for 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.

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 75% of VIPomas and approximately 50% 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.
Back to Top

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 of > 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. Medications used for acid suppression could falsely elevate gastrin levels and should be discontinued before testing.

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 diabetes.

Somatostatinomas

These tumors are rare and are associated with elevated blood glucose levels, achlorhydria, cholelithiasis, and diarrhea.
Back to Top

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.
Because of the limited success of preoperative localization tests, and because 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 for the MEN-1 syndrome, in which multiple small insulinomas are involved.

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.
Back to Top

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 multiple secondary tumors.

Surgery for gastrinoma-ZES

The ideal treatment for 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(Drug information on 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, because 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. Surgical resection of liver metastases is controversial; even more controversial is orthotopic liver transplantation. 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, protect hepatic function, and provide palliation in patients with hormonal production.
Surgical resection for nonfunctioning tumors is indicated and should be performed wth a goal of negative soft tissue and pancreatic margins. Due to the variable aggressive patterns of these tumors, there has been an interest in maximal debulking.

Radiation therapy for PETs

Adjuvant therapy. There is no established role for adjuvant therapy after tumor resection of PETs. Anecdotal reports indicate that 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(Drug information on interferon alfa-2a) and alfa-2b (Roferon-A, Intron A, respectively), 5-FU, doxorubicin, dacarbazine(Drug information on dacarbazine), and streptozocin.
Two randomized placebo-controlled phase III trials for patients with advanced, lower-grade pancreatic neuroendocrine tumors have been reported. Everolimus (Afinitor) compared to placebo (Yao JC et al: *N Engl J Med* 2011) demonstrated superior progression-free survival (11 months vs 4.6 months, $P < .001$). Simarily, another randomized (Raymond E et al: *N Engl J Med* 2011), phase III trial of sunitinib (Sutent) compared with placebo for advanced pancreatic neuroendocrine tumors reported a significant improvement in progression-free survival favoring sunitinib (11.4 months vs 5.5 months, respectively; $P < .0001$).

Combination regimens. Combination chemotherapy is often more effective than 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 streptozocin alone (63% vs 36%), as well as a better complete response rate (33% vs 12%) and median survival duration (26 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 in PETs. Etoposide(Drug information on 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(Drug information on temozolomide) (Temodar) and with 5-FU, leucovorin, and oxaliplatin (FOLFOX) chemotherapy, temozolomide with capecitabine, sorafenib(Drug information on sorafenib) (Nexavar), vatalanib, imatinib(Drug information on imatinib) (Gleevec), thalidomide(Drug information on thalidomide) (Thalomid), and the mTOR inhibitors everolimus (Afinitor) and temsirolimus (Torisel). Sunitinib and everolimus have been approved by the US Food and Drug Administration for the treatment of pNETs.

Treatment of symptoms

Octreotide. As discussed more fully in the section on carcinoid tumors, a promising experimental approach for patients whose tumors express somatostatin receptors is the use of octreotide conjugated to a therapeutic radioisotope.
Other agents. Omeprazole(Drug information on omeprazole) (Prilosec), an inhibitor of the function of the parietal cell hydrogen pump, is more effective than histamine type 2 (H_2)-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 injectable diazoxide(Drug information on 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.
Bisphosphonate therapy should be considered for patients with bone metastases.
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 main portal vein is required for this procedure.
Other liver-directed therapeutic strategies include radiofrequency ablation (RFA) for select patients and ^{90}yttrium microspheres.

- **TABLE OF CONTENTS**
- **Pancreatic Cancer**
- **Pancreatic Cystic Neoplasms**
- **Pancreatic Endocrine Tumors**
- **Carcinoid Tumors of the GI Tract**
- Signs and Symptoms
- Diagnosis
- Staging and Prognosis
- Treatment
- **Adrenocortical Carcinoma**
- **Pheochromocytoma**
- **Suggested Reading**

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 the 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(Drug information on 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.

Back to Top

Signs and Symptoms

Symptoms of carcinoid tumors are often long-term and vague. The majority of patients diagnosed with carcinoid tumors can have their symptoms (of varying intensity) tracked for one year prior.

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 nearsyncope and hypotension. Diarrhea

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.

Cardiac 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. Because the disease remains undiagnosed in many patients, a cardiac evaluation should be performed in all patients who have carcinoid syndrome.

Symptom triad

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

Back to Top

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-[Phe1]-octreotide. Other scans of increasing interest include ^{68}Ga-DOTA-1-Nal^{3}-octreotide (^{68}Ga-DOTANOC) and ^{68}Ga-DOTA-D-Phe^{1}-Tyr^{3}-octreotate (^{68}Ga-DOTATATE). PET scans are rarely useful, particularly in well differentiated or moderately differentiated tumors.

Back to Top

TABLE 3 TNM staging of neuroendocrine tumors

Staging and Prognosis

Staging

Carcinoid tumors are staged according to local spread of disease, nodal status, and distant metastatic involvement, using the AJCC TNM system (**Table 3**).

The site of tumor origin is potentially prognostic, because 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.

• *Gastric carcinoids*—Types I and II are often multifocal, associated with an elevated gastrin level, and relatively indolent, whereas type III gastric carcinoids are solitary, have a normal gastrin level, and have a more aggressive clinical course.
Back to Top

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.
Small intestines and rectal carcinoids should be resected with a wedge lymphadenectomy 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*—Liver transplantation may be of benefit in highly select patients without extrahepatic disease whose cancer progresses after other therapeutic interventions.
Preoperative and intraoperative considerations. All patients with metastatic, hormonally active carcinoid tumors require echocardiograms before any surgical intervention to evaluate for valvular disease. Furthermore, patients will require preoperative treatment with octreotide either subcutaneously or intravenously. Administration of intravenous octreotide is the preferred method of managing carcinoid crisis. All patients undergoing operative intervention should have a cholecystectomy, because octreotide use can promote the development of gallstones. Also, regional therapy for the liver with the use of embolic material, can cause acute cholecystitis.
Radiation. Carcinoid tumors are modestly responsive to radiation therapy and frequently are 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%).
A single-arm study (Bushnell JL Jr. et al: *J Clin Oncol* 2010) of ^{90}yttrium-edotreotide administered to 90 symptomatic patients with carcinoid tumor refractory to octreotide resulted in stable disease or response for 74% of patients.
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 (Sutent), sorafenib (Nexavar), 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(Drug information on interferon alfa-2b) vs depot octreotide plus bevacizumab in advanced carcinoid patients with poor prognoses.
Management of poorly differentiated (high-grade or anaplastic) neuroendocrine tumors and metastatic disease and postresection therapy for isolated resectable disease consists of the same systemic treatment as that used for small-cell lung cancer.

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. The most commonly used dose and schedule of somatostatin in the depot formulation is given at monthly doses of 20 mg or higher.

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(Drug information on lanreotide), pasireotide and vapreotide, are under investigation. A sustained-release formulation of lanreotide (Somatuline Depot) is specifically indicated for the long-term treatment of patients with acromegaly who have responded inadequately to surgery and/or radiotherapy or for whom surgery and/or radiotherapy is not an option.
Patients who demonstrate disease resistance with somatostatin analog treatment alone may benefit from combination therapy with interferon-alfa 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, ^{111}indium or ^{90}yttrium or 177 lutetium) 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 (H_1)- and H_2-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.
Bisphosphonate therapy should be considered for patients with bone metastases.
Hepatic arterial embolization. Hepatic arterial embolization with such products 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 ^{90}yttrium microspheres.

- **TABLE OF CONTENTS**
- **Pancreatic Cancer**
- **Pancreatic Cystic Neoplasms**
- **Pancreatic Endocrine Tumors**
- **Carcinoid Tumors of the GI Tract**
- **Adrenocortical Carcinoma**
- Etiology
- Signs and Symptoms
- Staging and treatment
- **Pheochromocytoma**
- **Suggested Reading**

ADRENOCORTICAL CARCINOMA

Adrenocortical carcinoma is a rare, highly malignant neoplasm that accounts for about 0.2% of cancer deaths. Long-term survival is poor 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 (eg, multiple neoplasia type I, Li-Fraumeni syndrome, or Beckwith-Wiedemann 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.
Back to Top

Staging and Treatment

Adrenal gland tumors are staged according to local spread of disease, nodal status, and distant metastatic involvement, using the AJCC TNM system (**Table 4**).

TABLE 4 TNM staging of adrenal gland tumors

Surgery

Complete surgical resection is the treatment of choice in patients with localized disease, because it offers the best chance of extending the disease-free interval and survival.
Although laparoscopic adrenalectomy is often utilized for adenomas, its role in the management of adrenocortical cancer is controversial. Recent data have shown worse outcomes following laparoscopic resections, compared with open resections. Any disruption of the tumor capsule can lead to peritoneal dissemination; therefore, the open technique is often used.
Following resection, the role of adjuvant therapy is unknown, with no prospective data available. A retrospective study suggests that adjuvant treatment with mitotane (Lysodren) improves recurrence-free survival. Owing to the study methodology, however, the conclusions are not universally accepted.

Medical therapy

Mitotane. 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 dosage is variable.
Chemotherapy. Limited studies of combination chemotherapy regimens, including cisplatin/etoposide/mitotane, cisplatin/etoposide/doxorubicin/mitotane, and streptozocin/mitotane, have demonstrated responses of between 35% and 50%. A recent randomized trial of 304 patients with advanced adrenocorical carcinoma compared mitotane with etoposide, doxorubicin and cisplatin vs mitotane and streptozocin. There was no difference in survival; however, the three-drug combination produced superior response (23.2% vs 9.2%, $P < .001$) and progression-free survival (5 months vs 2.1 months, $P < .001$). The preferred treatment approach remains participation in a clinical trial, when available.
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 antifungal 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.

- **TABLE OF CONTENTS**
- **Pancreatic Cancer**
- **Pancreatic Cystic Neoplasms**
- **Pancreatic Endocrine Tumors**
- **Carcinoid Tumors of the GI Tract**
- **Adrenocortical Carcinoma**
- **Pheochromocytoma**
- Epidemiology and Etiology
- Signs and Symptoms
- Diagnosis
- Treatment
- **Suggested Reading**

PHEOCHROMOCYTOMAS

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% 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% of pheochromocytomas are either 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.
Back to Top

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. Genetic testing is recommended for patients suspected of having MEN-2.
Back to Top

Signs and Symptoms

Patients can present with various symptoms, ranging from mild labile hypertension to hypertensive crisis, myocardial infarction, or cerebral vascular accident, most 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.
Back to Top

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 done; 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. A 131 iodine-metaiodobenzylguanidine (MIBG) scan and somatostatin receptor scintigraphy (SRS) provide "functional" images; 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 131 iodine-MIBG scan constitute diagnostic proof.
Back to Top

Treatment

Preoperative medical management

Phenoxybenzamine (Dibenzyline), an oral, long-acting, noncompetitive alpha-adrenoceptor blocker, is a helpful, widely used 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-blocker 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 of 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 using streptozocin-based regimens or the combination of cyclophosphamide, vincristine, and dacarbazine has yielded promising responses. Treatment with 131-iodine-MIBG or with radiolabeled somatostatin (in Europe) 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 crises ensue.
Surgery. In cases in which limited and resectable lesions can be identified, surgery can effect complete and lasting remission of the disease.

- **TABLE OF CONTENTS**
- **Pancreatic Cancer**
- **Pancreatic Cystic Neoplasms**
- **Pancreatic Endocrine Tumors**
- **Carcinoid Tumors of the GI Tract**
- **Adrenocortical Carcinoma**
- **Pheochromocytoma**
- **Suggested Reading**

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