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Pancreatic Adenocarcinoma

Clinical Practice Guidelines in Oncology

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Overview

An estimated 36,800 people will die of pancreatic cancer in the United States in 2010.1 This disease is the fourth most common cause of cancer-related death among men and women in the United States.[1] Its peak incidence occurs in the seventh and eighth decades of life. Although incidence is roughly equal for the sexes, African Americans seem to have a higher incidence of pancreatic cancer than white Americans.2 These guidelines only discuss tumors of the exocrine pancreas; neuroendocrine tumors are not included.

NCCN Clinical Practice Guidelines in Oncology on Pancreatic Adenocarcinoma

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, pancreas, adenocarcinoma, ductal carcinoma, endoscopic retrograde cholangiopancreatography, ultrasonography, gemcitabine, (*JNCCN* 2010;8:972–1017)

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines™ is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Guidelines Panel for Pancreatic Adenocarcinoma

At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Guidelines on Pancreatic Adenocarcinoma panel members can be found on page 1017. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, please visit www.NCCN.org.

By definition, these NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the panel members during development of these guidelines. A 5% rule (omitting clinical scenarios that constitute fewer than 5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from these guidelines. The panel unanimously endorses participation in a clinical trial as the preferred option over standard or accepted therapy.

Risk Factors and Genetic Predisposition

Although the associated increase in risk is small, the development of pancreatic cancer is firmly linked to cigarette smoking.[3–5] Some evidence shows that increased consumption of red meat and dairy products is associated with an elevation in pancreatic cancer risk,[6] although other studies have failed to identify dietary risk factors.[4] An increased body mass index is also associated with increased risk.[7–9] Occupational exposure to chemicals, such as beta-naphthylamine and benzidine, is also associated with an increased risk of pancreatic cancer.[10]

The relationship among diabetes mellitus, alcohol intake, and chronic pancreatitis with adenocarcinoma of the pancreas has been a topic of considerable debate. Numerous studies have shown an association between new-onset diabetes and the development of pancreatic cancer.[11–13] However, certain risk factors, such as obesity, and the use of

Text continues on p. 991

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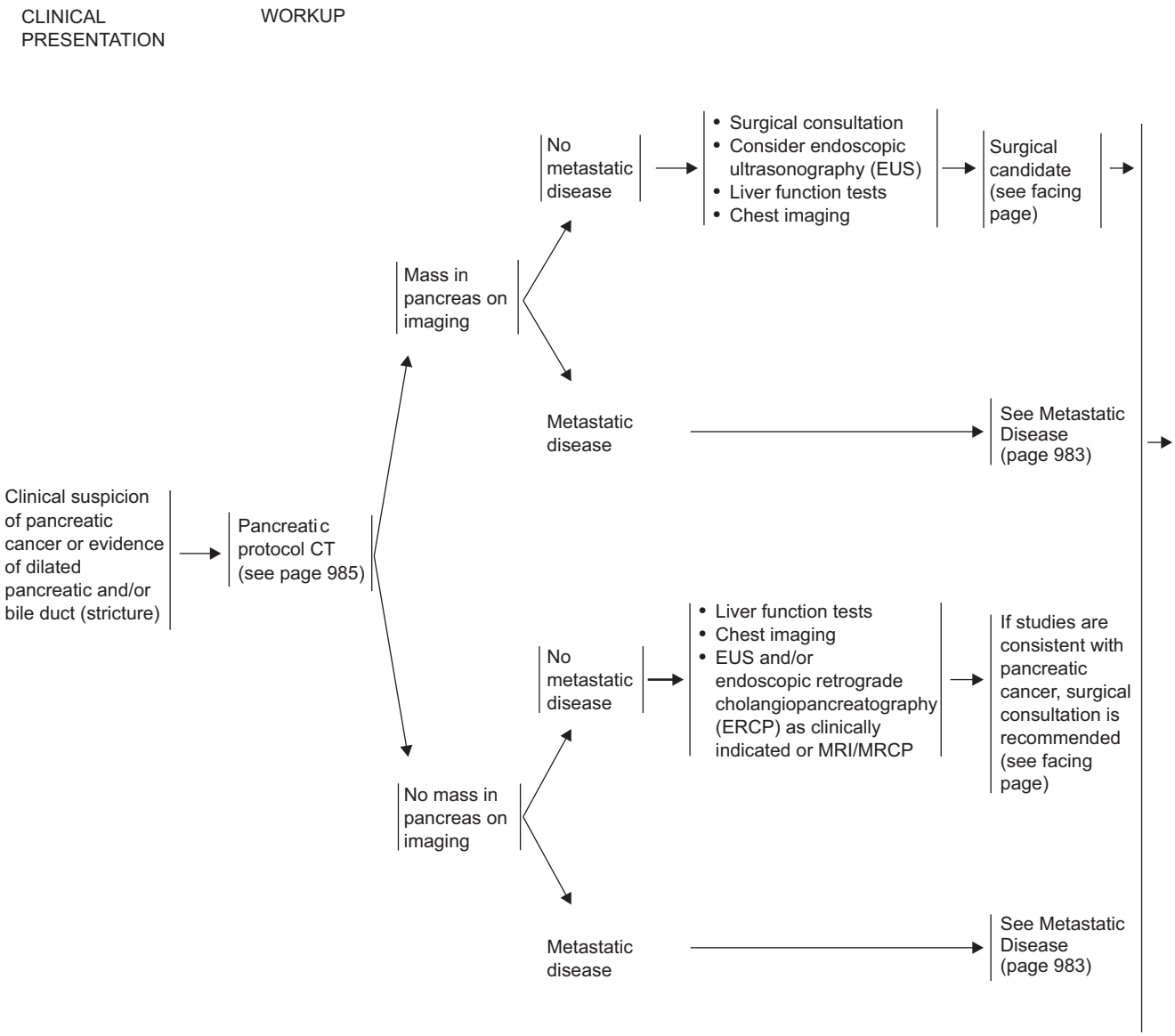

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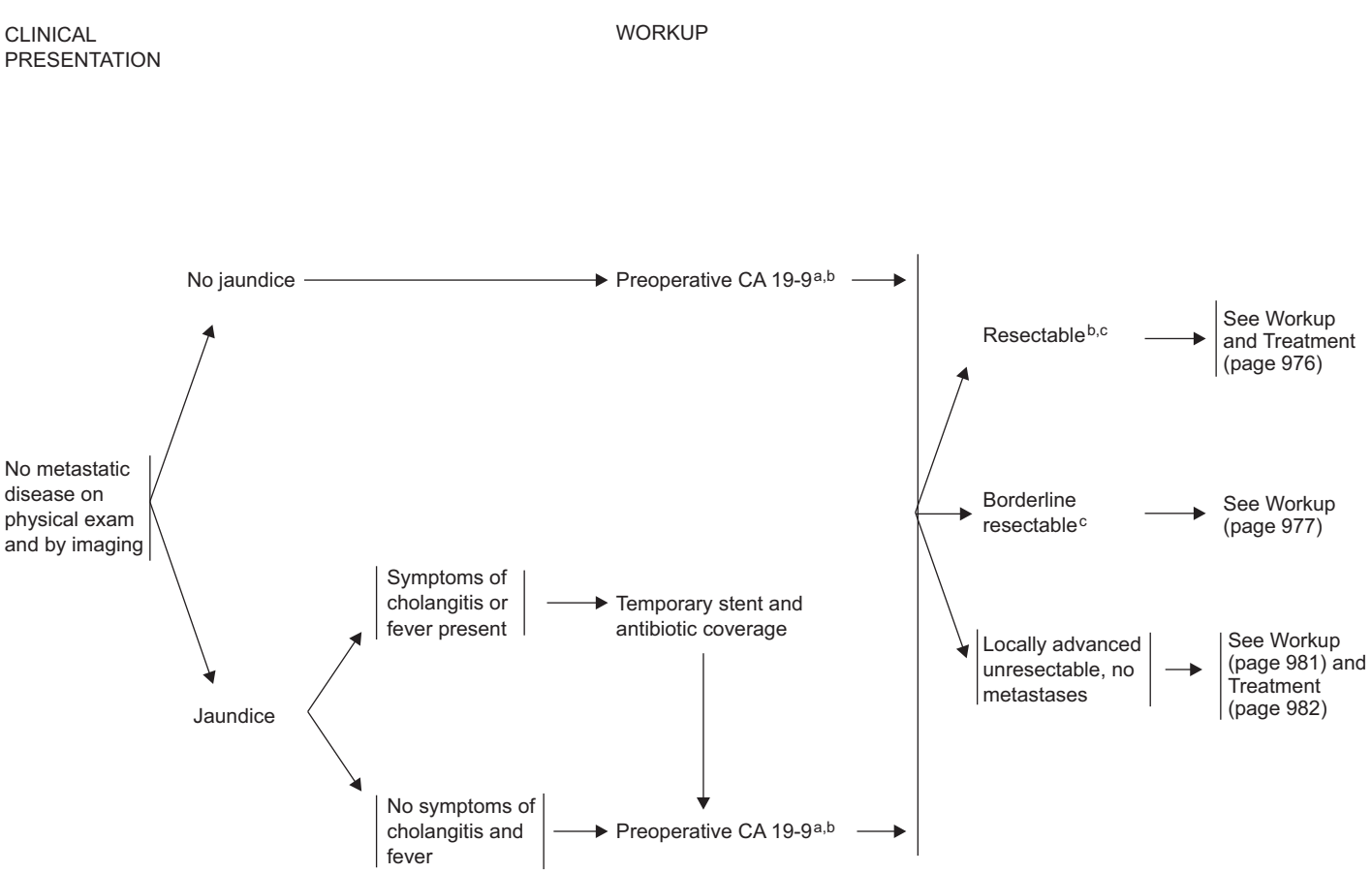
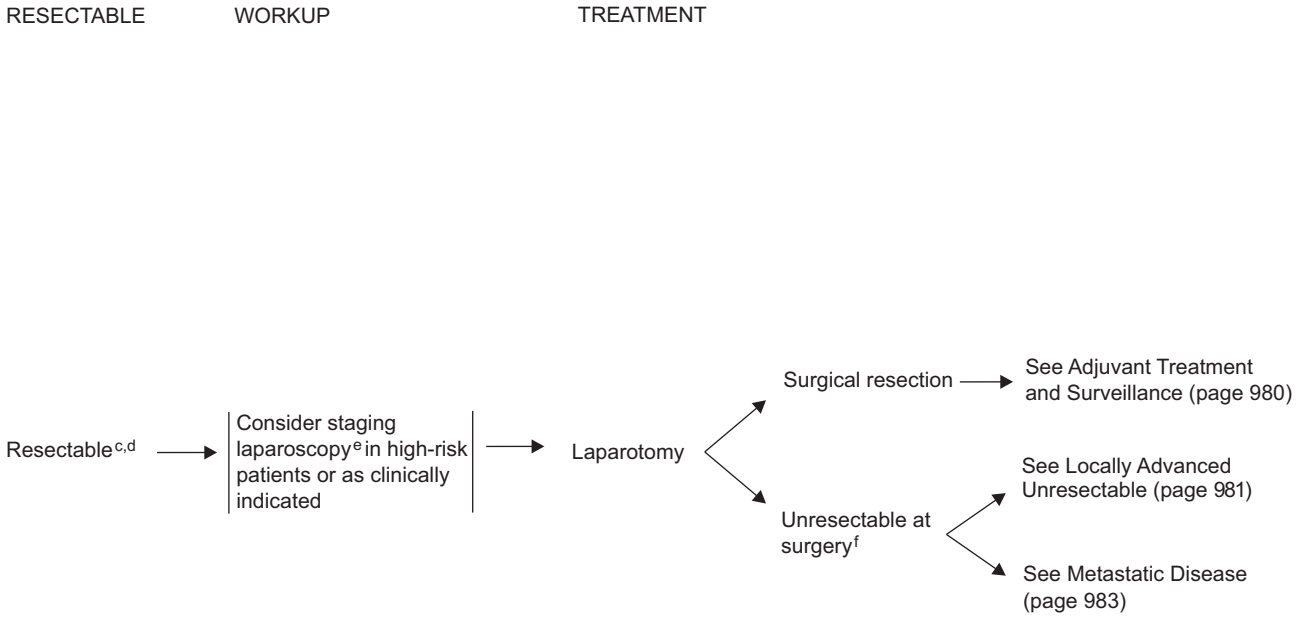


[a] CA 19-9 may be elevated in cases of benign biliary obstruction and does not represent an appropriate baseline until the patient is decompressed. In addition, CA19-9 may be undetectable in Lewis-a negative individuals.
[b] See Principles of Diagnosis and Staging (page 985).
[c] See Criteria Defining Resectability Status (page 986).



[c] See Criteria Defining Resectability Status (page 986).
[d] Consider neoadjuvant therapy on clinical trial.
[e] See Principles of Diagnosis and Staging #6 (page 985).
[f] See Principles of Palliation and Supportive Care (page 987).

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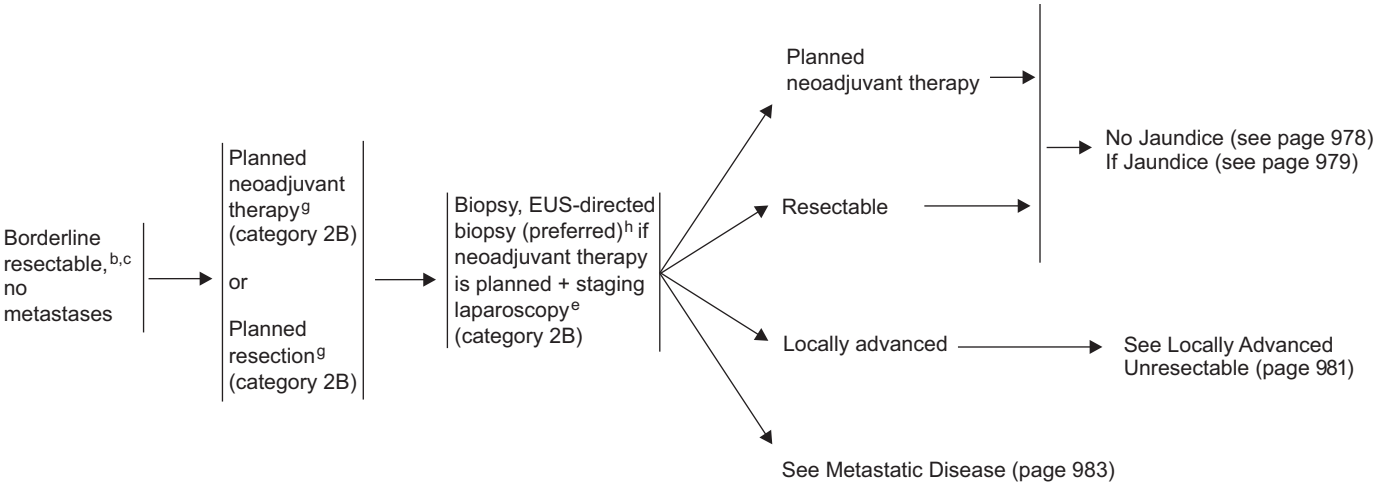
BORDERLINE RESECTABLE, NO METASTASES

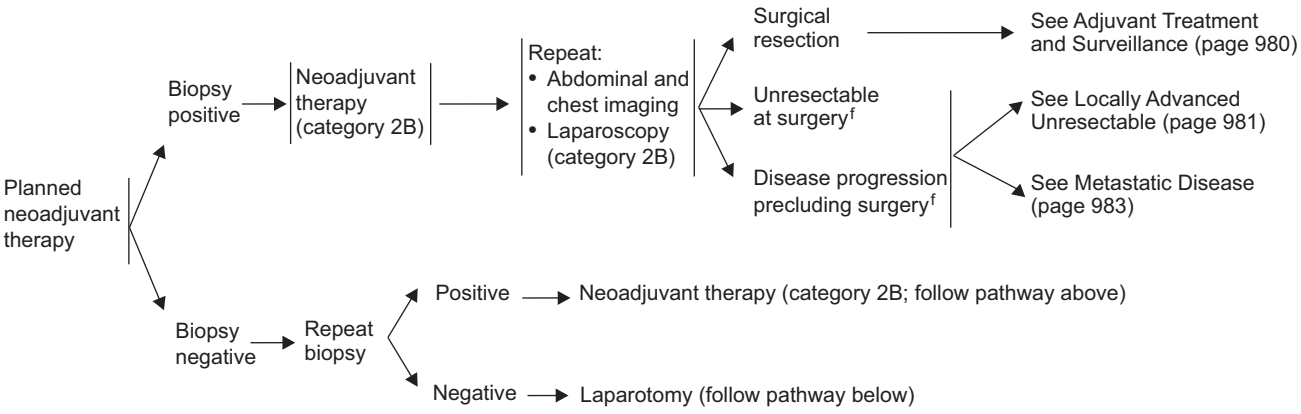
WORKUP

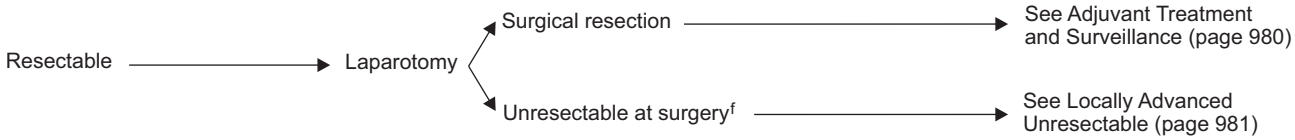


[b] See Principles of Diagnosis and Staging (page 985).
[c] See Criteria Defining Resectability Status (page 986).
[e] See Principles of Diagnosis and Staging #6 (page 985).
[g] Most NCCN institutions prefer neoadjuvant therapy in the setting of borderline resectable disease at a high-volume center. Performing surgery with a high likelihood of a positive margin is not recommended.
[h] See Principles of Diagnosis and Staging #1 and #5 (page 985).

BORDERLINE RESECTABLE
NO METASTASES, NO JAUNDICE

TREATMENT



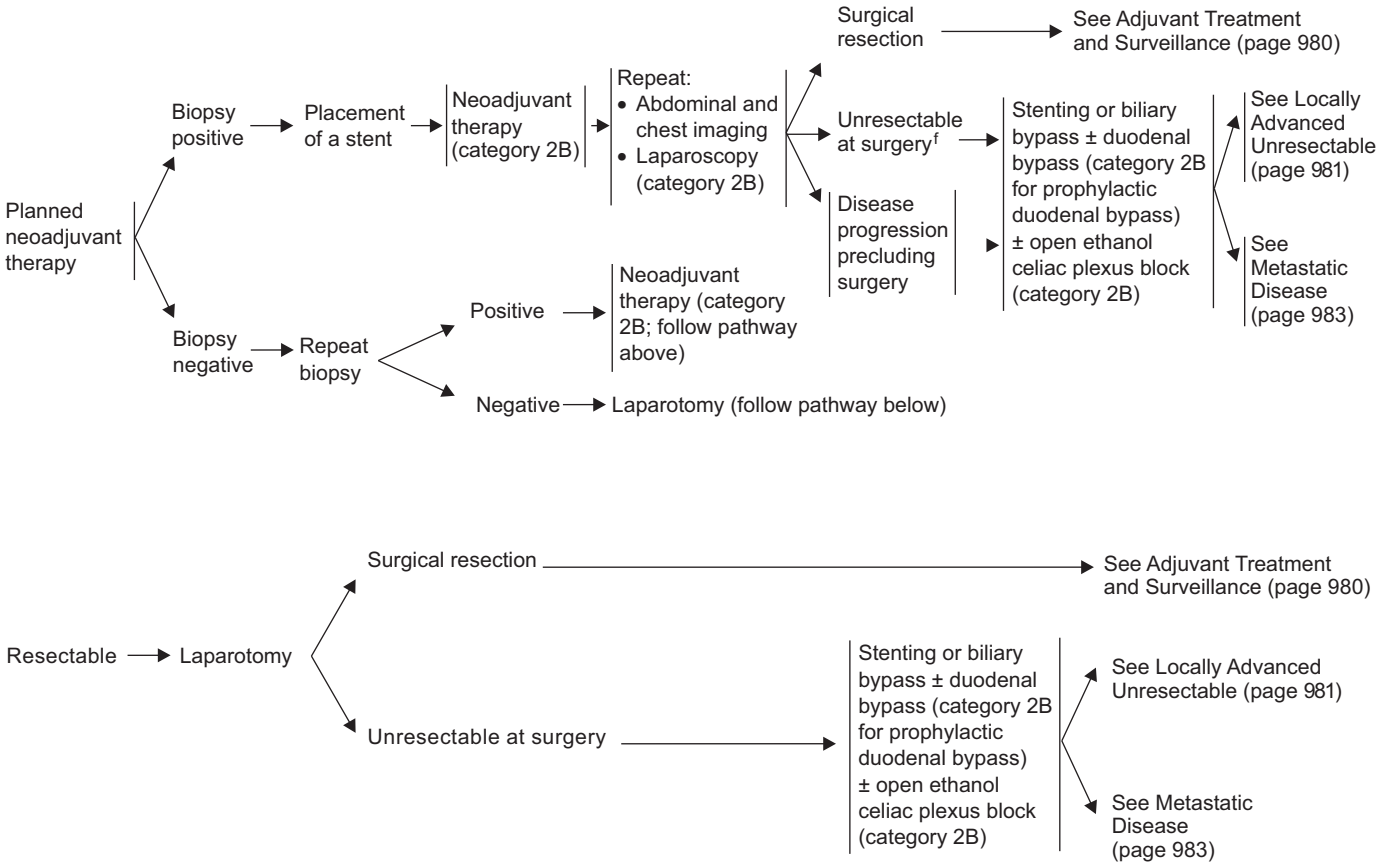


[f] See Principles of Palliation and Supportive Care (page 987).

Pancreatic Adenocarcinoma Version 2:2010

BORDERLINE RESECTABLE
NO METASTASES,JAUNDICE

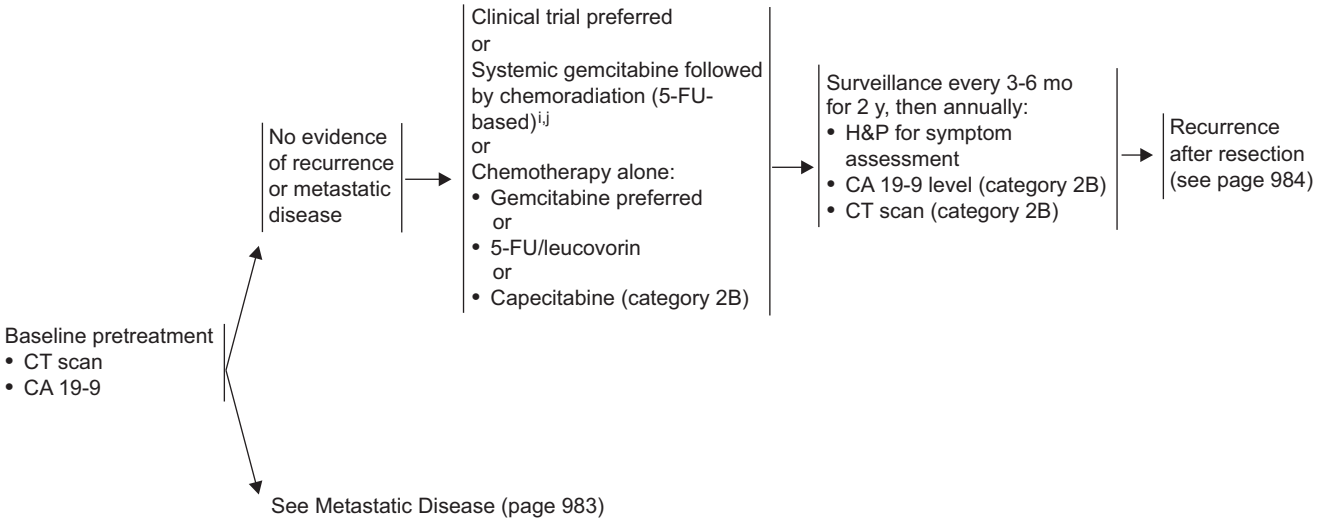
TREATMENT



[f]See Principles of Palliation and Supportive Care (page 987).

POSTOPERATIVE ADJUVANT TREATMENT [i]

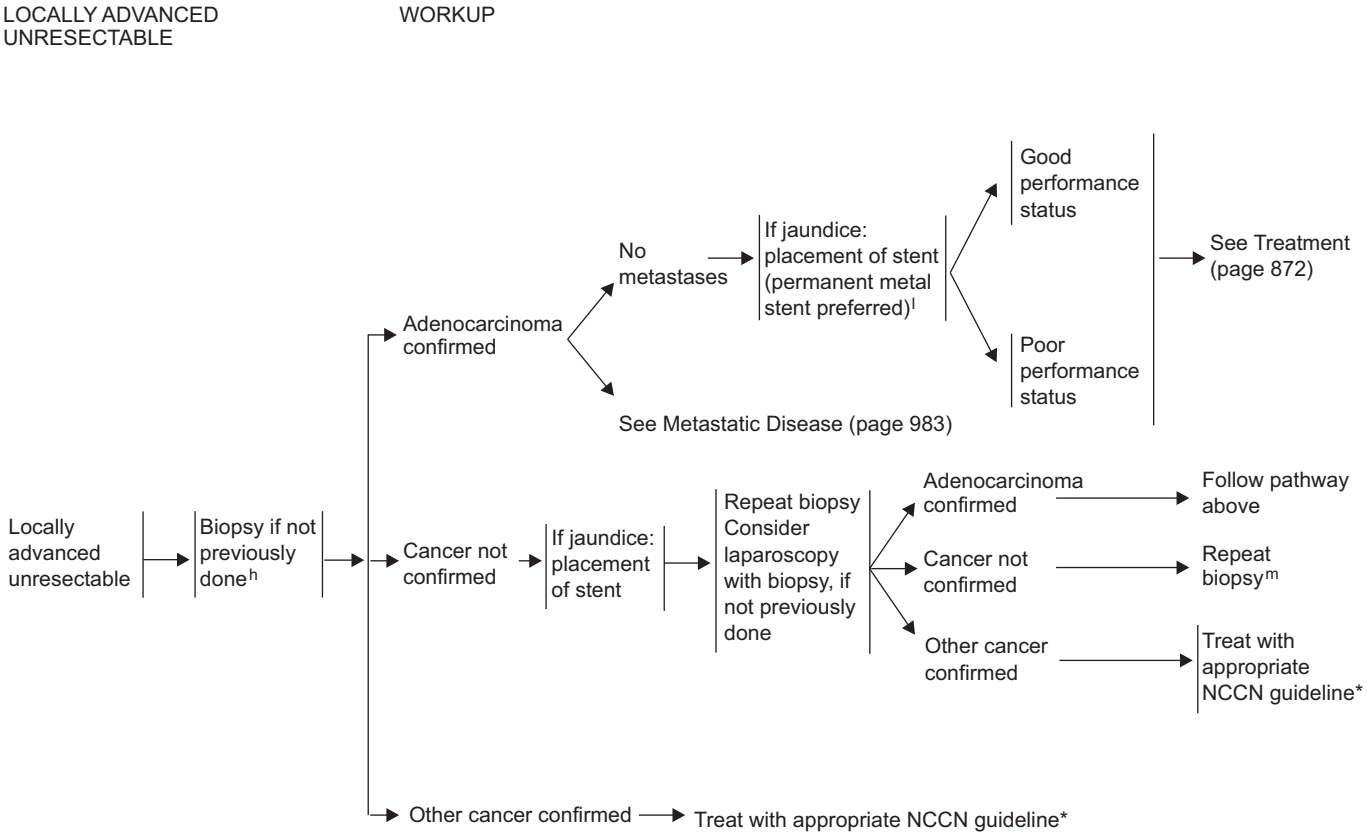
SURVEILLANCE



[i] Adjuvant treatment should be administered to patients who have not undergone neoadjuvant therapy and have adequately recovered from surgery; treatment should be initiated within 4 to 8 wk. If systemic chemotherapy precedes chemoradiation, restaging with a CT scan should be performed after each treatment modality. Patients who have undergone neoadjuvant chemoradiation or chemotherapy are candidates for further adjuvant therapy after surgery.

[j] See Principles of Radiation Therapy (page 988).

Pancreatic Adenocarcinoma Version 2:2010



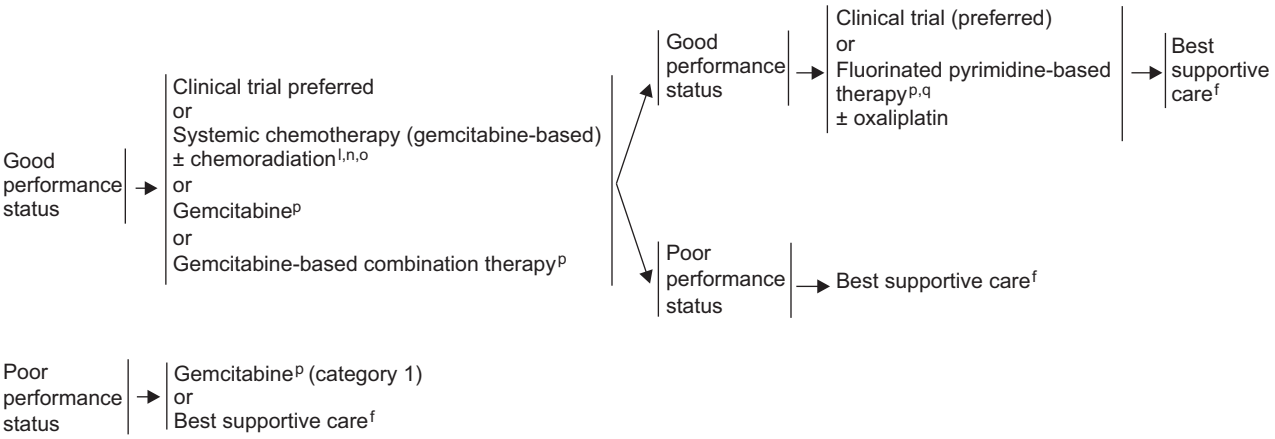
*To view the NCCN Clinical Practice Guidelines in Oncology list of contents, visit the NCCN Web site at www.NCCN.org.

[h] See Principles of Diagnosis and Staging #1 and #5 (page 985).
[l] Unless biliary bypass performed at laparoscopy or laparotomy.
[m] In this situation, a laparscopic-directed biopsy may be useful.

LOCALLY ADVANCED UNRESECTABLE

TREATMENT

SALVAGE THERAPY



[f]See Principles of Palliation and Supportive Care (page 987).
[l]See Principles of Radiation Therapy (page 988).
[n]Laparoscopy as indicated to evaluate distant disease.
[o]Chemoradiation should be reserved for patients who do not develop metastatic disease while undergoing systemic chemotherapy. Patients with a significant response to chemoradiation may be considered for surgical resection, although no definitive evidence currently supports this intervention.
[p]See Principles of Chemotherapy (pages 989 and 990).
[q]For fluorinated pyrimidine-naive patients. Gemcitabine is also an option for those who received 5-FU chemoradiation and no additional chemotherapy.

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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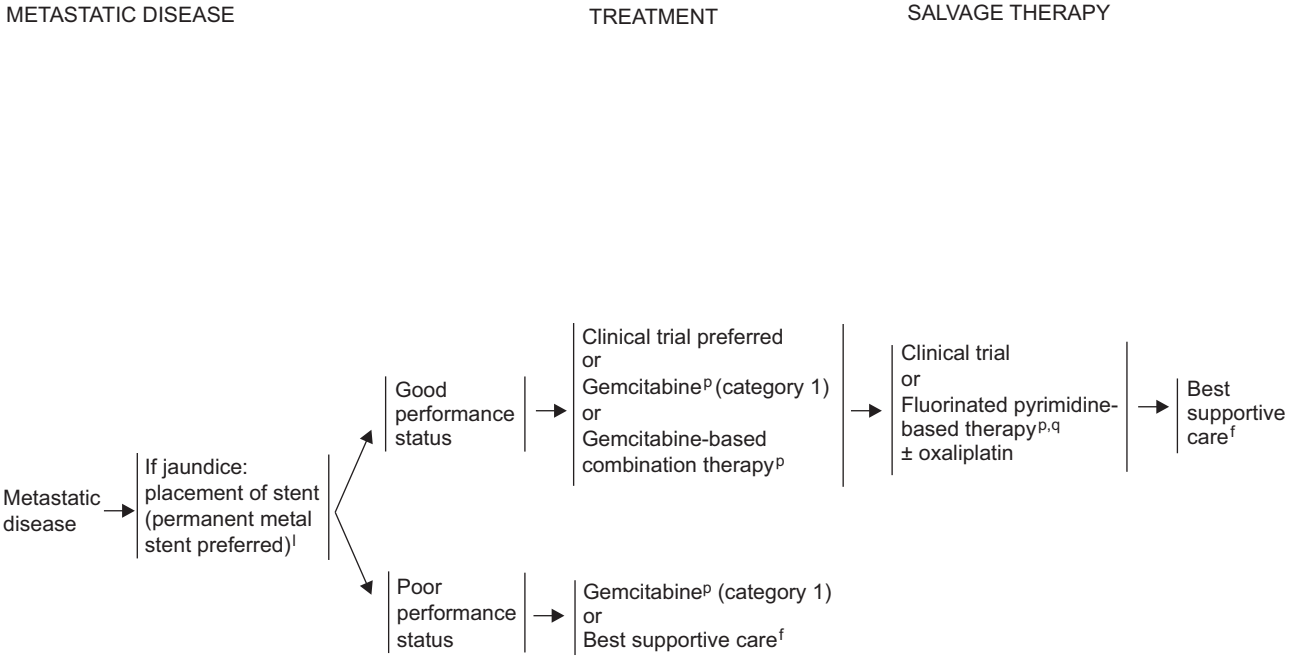

[f] See Principles of Palliation and Supportive Care (page 987).
[l] Unless biliary bypass performed at laparoscopy or laparotomy.
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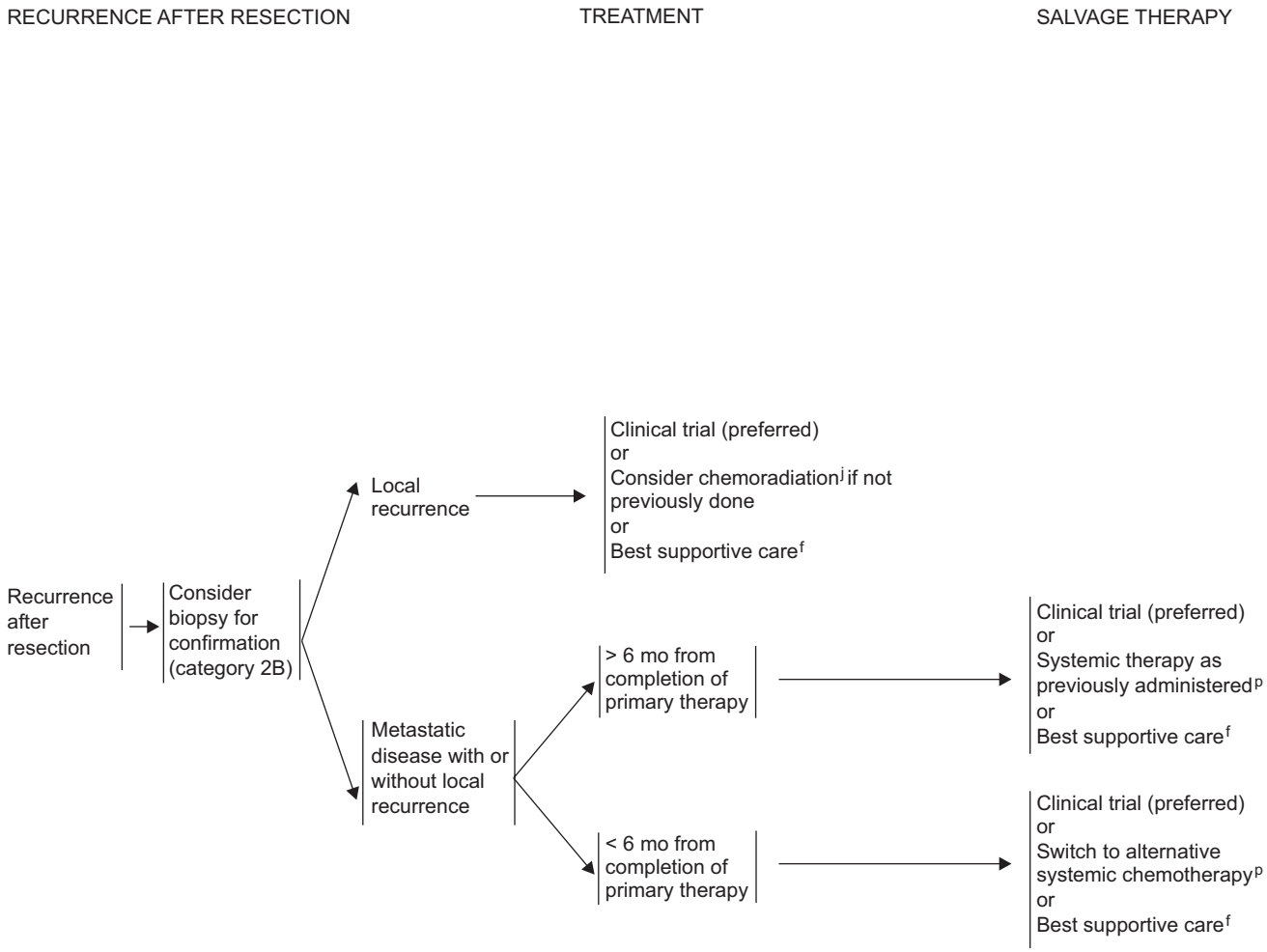

[f]See Principles of Palliation and Supportive Care (page 987).
[j]See Principles of Radiation Therapy (page 988).
[p]See Principles of Chemotherapy (pages 989 and 990).

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Pancreatic Adenocarcinoma Version 2:2010

PRINCIPLES OF DIAGNOSIS AND STAGING

#1: Decisions about diagnostic management and resectability should involve multidisciplinary consultation with reference to appropriate radiographic studies to evaluate the extent of disease. Resections should be done at institutions that perform a large number (15-20) of pancreatic resections annually.

#2: Imaging should include specialized pancreatic CT scan. CT should be performed according to a defined pancreas protocol, such as triphasic cross-sectional imaging and thin slices.

#3: The role of PET/CT scan remains unclear. PET/CT scan may be considered after formal pancreatic CT protocol in "high-risk" patients to detect extrapancreatic metastases. It is not a substitute for high-quality contrast-enhanced CT.

#4: Endoscopic ultrasound (EUS) may be complementary to CT for staging.

#5: EUS-directed FNA biopsy is preferable to a CT-guided FNA in patients with resectable disease because of lower risk of peritoneal seeding with EUS-FNA than with the percutaneous approach. Biopsy proof of malignancy is not required before surgical resection, and a nondiagnostic biopsy should not delay surgical resection when the clinical suspicion for pancreatic cancer is high.

#6: Diagnostic staging laparoscopy to rule out subradiologic metastases (especially for body and tail lesions) is routinely used in some institutions before surgery or chemoradiation, or selectively in patients who are at higher risk for disseminated disease (borderline resectable disease, markedly elevated CA 19-9, large primary tumors, or large regional lymph nodes).

#7: Positive cytology from washings obtained at laparoscopy or laparotomy is equivalent to M1 disease. If resection has been performed for such a patient, they should be treated as for M1 disease.

CRITERIA DEFINING RESECTABILITY STATUS

Tumors considered localized and resectable should demonstrate the following:

- No distant metastases
- No radiographic evidence of superior mesenteric vein (SMV) and portal vein abutment, distortion, tumor thrombus, or venous encasement
- Clear fat planes around the celiac axis, hepatic artery, and superior mesenteric artery (SMA)

Tumors considered borderline resectable include the following:

- No distant metastases
- Venous involvement of the SMV/portal vein showing tumor abutment with or without impingement and narrowing of the lumen, encasement of the SMV/portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction
- Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis
- Tumor abutment of the SMA not to exceed 180° of the circumference of the vessel wall

The NCCN Pancreatic Adenocarcinoma Panel recognizes the work of the experts and adapt their criteria to define resectability status. Callery MP, Chang KJ, Fishman EK, et al. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol 2009;16:1727-1733.

Tumors considered to be unresectable show the following:

- Head
  - Distant metastases
  - > 180° SMA encasement, any celiac abutment
  - Unreconstructible SMV/portal occlusion
  - Aortic invasion or encasement
- Body
  - Distant metastases
  - SMA or celiac encasement > 180°
  - Unreconstructible SMV/portal occlusion
  - Aortic invasion
- Tail
  - Distant metastases
  - SMA or celiac encasement > 180°
- Nodal status
  - Metastases to lymph nodes beyond the field of resection should be considered unresectable

Pancreatic Adenocarcinoma Version 2:2010

PRINCIPLES OF PALLIATION AND SUPPORTIVE CARE

Objective: Prevent and ameliorate suffering while ensuring optimal quality of life

- Biliary obstruction
  - Endoscopic biliary stent (preferred method)
  - Percutaneous biliary drainage with subsequent internalization
  - Open biliary-enteric bypass
- Gastric outlet obstruction
  - Good performance status
    - Gastrojejunostomy (open or laparoscopic) ± J-tube
    - Consider enteral stent[1]
  - Poor performance status
    - Enteral stent[1]
    - PEG tube
- Severe tumor-associated abdominal pain
  - EUS-guided celiac plexus neurolysis (fluoroscopic- or CT-guided if unavailable)
  - Consider palliative chemoradiation if not already given as part of primary therapy regimen
- Depression, pain, malnutrition
  - Formal palliative medicine service evaluation when appropriate (see NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Supportive Care*)
- Pancreatic insufficiency
  - Pancreatic enzyme replacement
- Thrombembolic disease
  - Low-molecular weight heparin preferred over warfarin

*To view the various NCCN Clinical Practice Guidelines in Oncology on Supportive Care, visit the NCCN Web site at www.NCCN.org.

[1] Placement of an enteral stent is particularly important for patients with poor performance status.

PRINCIPLES OF RADIATION THERAPY

IMRT is being increasingly applied for therapy of pancreatic adenocarcinoma. No clear consensus exists on appropriate maximum dose of radiation in either the adjuvant setting or the setting of locally advanced disease.

Neoadjuvant/Adjuvant RT

In contrast to the GITSG trial,[1,2] more recent phase III trials have not provided evidence of benefit from radiotherapy in this setting. A recent trial, ESPAC-1, has even suggested that radiotherapy is detrimental.[3] However, these trials have been widely criticized for lack of statistical power (EORTC)[4] and inadequate quality control (ESPAC). Therefore, 5-FU-based chemoradiotherapy as part of adjuvant therapy remains an acceptable choice.

- Use of CT simulation and 3-dimensional (3-D) treatment planning is strongly encouraged.
- Treatment volumes should be based on preoperative CT scans and surgical clips (when placed).
- Treatment volumes include the location of the primary tumor and regional lymph nodes.
- Dose: 45-54 Gy (1.8-2.0 Gy/d).

Definitive RT for Unresectable Tumors

Radiation is usually given in combination with 5-FU chemotherapy. Recent evidence suggests that concurrent gemcitabine and radiation can yield similar outcomes.

- Use of CT simulation and 3-D treatment planning is strongly encouraged.
- Treatment volumes should be based on CT scans and surgical clips (when placed).
- When 5-FU-based radiochemotherapy is used, treatment volumes include the location of the primary tumor and regional lymph nodes.
- The dose for definitive 5-FU-based radiochemotherapy is 50-60 Gy (1.8-2.0 Gy/d).

ITSG trial: Moertel CG, Frytak S, Hahn RG, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil. Cancer 1981;48:1705-1710.
alser, MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg 1985;20:899-903.
SPAC-1 trial: Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004;350:1200-1210.
ORTC trial: Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg 1999;230:776-782; discussion 782-784.

Pancreatic Adenocarcinoma Version 2:2010

PRINCIPLES OF CHEMOTHERAPY (1 of 2)

Systemic therapy is used in the neoadjuvant or adjuvant setting and in the management of locally advanced unresectable and metastatic disease.

- Goals of systemic therapy should be discussed with patients before initiation of therapy, and enrollment in a clinical trial is strongly encouraged.
- Close follow-up of patients undergoing chemotherapy is indicated.

Metastatic

- Gemcitabine at 1000 mg/m^2 over 30 min, weekly for 3 wk every 28 d, is considered standard front-line therapy for patients with metastatic disease (category 1).
- Fixed-dose rate gemcitabine (10 mg/m^2/min) may substitute for standard infusion of gemcitabine over 30 min (category 2B).
- Gemcitabine combinations have shown a favorable or potentially favorable impact on time to progression or survival (overall or 1 y) for patients with good performance status:
  - Gemcitabine + erlotinib[1]
  - Gemcitabine + cisplatin
  - Fixed-dose rate gemcitabine + oxaliplatin[2]
  - Gemcitabine + fluoropyrimidine[3]
- Second-line therapy may consist of gemcitabine for patients not previously treated with the drug. Other options include capecitabine[4] (1000 mg/m^2 by mouth twice daily, days 1-14 every 21 d), 5-FU/leucovorin,[5] or CapeOx.[6] Results of the CONKO-003 trial showed a significant improvement in overall survival with addition of oxaliplatin to 5-FU/leucovorin.

Locally Advanced

- Gemcitabine or gemcitabine-based combination therapy may be considered as initial therapy before 5-FU-based chemoradiation for patients with locally advanced, unresectable disease. Patients whose metastatic disease progresses are not candidates for chemoradiation unless required for palliative purposes.

Adjuvant

- The CONKO-001 trial showed significant improvements in disease-free and overall survival with use of postoperative gemcitabine as adjuvant chemotherapy versus observation in resectable pancreatic adenocarcinoma.[7]
- ESPAC-3 study results showed no significant difference in overall survival between 5-FU/leucovorin versus gemcitabine after surgery. When the groups receiving adjuvant 5-FU/leucovorin and adjuvant gemcitabine were compared, median survivals were 23.0 and 23.6 months, respectively.[8]
- Gemcitabine-based chemotherapy is frequently combined, sequentially, with 5-FU-based chemoradiotherapy.
- No significant differences were observed in the RTOG 97-04 study comparing pre- and postchemoradiation 5-FU with pre- and postchemoradiation gemcitabine for postoperative adjuvant treatment. However, overall survival was significantly increased in the gemcitabine arm compared with the 5-FU arm in the subset of patients with tumors of the pancreatic head.[9]

See references on page 990

PRINCIPLES OF CHEMOTHERAPY (2 of 2)

[1] Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer. A phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007;25:1960-1966.

[2] Heinemann V, Labianca R, Hinke A, et al. Increased survival using platinum analog combined with gemcitabine as compared to single agent gemcitabine in advanced pancreatic cancer: pooled analysis of two randomized trials, the GERCOR/GISCAD Intergroup study and German multicenter study. Ann Oncol 2007;18:1652-1659.

[3] Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine (GEM) versus gemcitabine plus capecitabine (GEM-CAP) in patients with advanced pancreatic cancer. J Clin Oncol 2009;27:5513-5518.

[4] Cartwright TH, Cohn A, Varkey JA, et al. Phase II study of oral capecitabine in patients with advanced or metastatic pancreatic cancer. J Clin Oncol 2002;20:160-164.

[5] Pelzer U, Kubica K, Stieler J, et al. A randomized trial in patients with gemcitabine refractory pancreatic cancer. Final results of the CONKO 003 study. J Clin Oncol 2008;26(Suppl 1):Abstract 4508.

[6] Xiong HQ, Varadhachary GR, Blais JC, et al. A phase II trial of oxaliplatin plus capecitabine (xelox) as second-line therapy for patients with advanced pancreatic cancer. Cancer 2008;113:2046-2052.

[7] Neuhaus P, Riess H, Post S, et al. CONKO-001: Final results of the randomized, prospective, multicenter phase III trial of adjuvant chemotherapy with gemcitabine versus observation in patients with resected pancreatic cancer [abstract]. J Clin Oncol 2008;26(Suppl 1):Abstract LBA 4504.

[8] Neoptolemos J, Buchler M, Stocken DD, et al. ESPAC-3 (2): a multicenter, international, open-label, randomized, controlled phase III trial of adjuvant 5-fluorouracil/folinic acid versus gemcitabine in patients with resected pancreatic ductal adenocarcinoma [abstract]. J Clin Oncol 2009;27(Suppl 1):Abstract LBA4505.

[9] Regine, WF Winter KA, Abrams RA, et al. Fluorouracil vs. gemcitabine chemotherapy before and after fluorouracil-based chemoradiation after resection of pancreatic adenocarcinoma. A randomized controlled trial. JAMA 2008;299:1019-1026.

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diabetic medications, can impact insulin resistance and blood glucose levels, thereby confounding these analyses.[14,15] Chronic pancreatitis has also been identified as a risk factor for pancreatic cancer.1[6,17] Nevertheless, further epidemiologic studies involving careful evaluation of these possible risk factors, with adjustments for potential confounders, are needed to clarify their impact on pancreatic cancer risk.

True familial pancreatic cancer is rare; however, a genetic predisposition may be present in up to 5% to 10% of patients,[18,19] and familial excess of pancreatic cancer is associated with high risk.[4,19] For example, a germline mutation of the *CDKN2A* (p16) gene has been reported in families with pancreatic cancer and melanoma.[20,21] An excess of pancreatic cancer is also seen in families harboring *BRCA2* (breast cancer susceptibility gene 2) mutations,[22,23] and particular mutations in the *PALB2* gene have recently been identified as possibly increasing pancreatic cancer susceptibility.[24] Asymptomatic individuals at high risk for pancreatic cancer (i.e., those with first-degree relatives with cancer) were assessed using endoscopic ultrasound (EUS) in the Cancer of the Pancreas Screening 2 (CAPS2) project. Preinvasive pancreatic neoplasms were detected, suggesting that EUS may have a promising role in screening high-risk patients.[25] The diagnostic yield of pancreatic cancer screening with EUS or MRI in asymptomatic individuals at high risk of having familial disease has also been investigated in 2 recent studies, although the malignant potential of some preinvasive pancreatic lesions and the impact of screening on survival are currently unclear.[26,27]

Diagnosis and Staging

Ductal adenocarcinoma and its variants account for more than 90% of pancreatic malignancies. The presenting symptoms of this disease can include weight loss, jaundice, floating stools, pain, dyspepsia, nausea, and depression; however, no early warning signs of pancreatic cancer have been established. As previously noted, sudden onset of adult type 2 diabetes in patients 50 years or older may be linked to a new diagnosis of pancreatic cancer; patients with long-standing diabetes may also develop pancreatic cancer.[28,29] Thus, pancreatic carcinoma should be considered in diabetic patients with unusual manifestations, such as abdominal symptoms and continuous weight loss. All NCCN Member Institutions represented on the panel agreed that all patients who have clinical suspicion of pancreatic cancer or evidence of a dilated duct (stricture) should undergo initial evaluation with dynamic-phase helical or spiral CT performed according to a defined pancreas protocol (see pages 974 and 975).[30,31]

Imaging Evaluations

CT is the most widely available and best-validated imaging modality for diagnosing and staging patients with pancreatic cancer.[32,33] A pancreas CT protocol involves triphasic (i.e., arterial, late arterial, and venous phases) cross-sectional imaging with thin slices using multidetector CT.[33,34] One rationale for triphasic CT is that the difference in contrast enhancement between the parenchyma and adenocarcinoma is highest during the late arterial phase, thereby providing a clear distinction between a hypodense lesion in the pancreas and the rest of the organ.

In addition to diagnosing pancreatic cancer, CT is the preferred modality to preoperatively distinguish between patients eligible for resection with curative intent and those with unresectable disease. Unlike many other cancers, CT imaging is the primary means of staging pancreatic cancer. The triphasic CT protocol allows for selective visualization of important arterial (e.g., celiac axis, superior mesenteric artery [SMA], peripancreatic arteries) and venous structures (e.g., superior mesenteric vein [SMV], splenic vein, portal vein), thereby allowing assessment of vascular invasion by tumor. Software allowing for 3-dimensional reconstruction of CT data can provide additional valuable information on the anatomic relationship between the pancreatic tumor and surrounding blood vessels and organs, although further development of this technology may be needed before it is routinely integrated into clinical practice.[35]

Studies have shown that 70% to 85% of patients determined with CT imaging to have resectable tumors were able to undergo resection.[33–38] The criteria for defining resectable disease with CT favor specificity over sensitivity to avoid denying surgery to patients with potentially resectable tumor.[33] Furthermore, the sensitivity of CT for small hepatic and peritoneal metastases is limited.

When CT is not possible or relatively contraindicated (e.g., allergy to contrast), MRI with gadolinium infusion can be used to diagnose and stage pancreatic cancer,[39,40] although MRI has not been shown

to perform better than CT in this setting. MRI can be a helpful adjunct to CT in the staging of pancreatic cancer, particularly for detecting the presence of extrapancreatic disease in high-risk patients.[41]

NCCN Member Institutions vary in the use of additional staging technologies, such as EUS. The role of EUS in staging is believed to be complementary to CT, providing additional information for patients whose CT scans show no lesion or who have questionable involvement of blood vessels or lymph nodes.[30] Because this procedure is operator-dependent, some divergence in use may occur because of differing technical capabilities and available expertise.

The usefulness of PET/CT for upstaging patients with pancreatic cancer has also been evaluated. In one retrospective study, the use of PET/CT following a standard CT protocol showed increased sensitivity for detecting metastatic disease compared with the standard CT protocol or PET/CT alone.[42] The sensitivity of detecting metastatic disease for PET/CT alone, standard CT alone, and the combination of PET/CT and standard CT was 61%, 57%, and 87%, respectively. In this study, the clinical management of 11% of patients with invasive pancreatic cancer was changed as a result of PET/CT findings. Nevertheless, the role of PET/CT in this setting is evolving and has not yet been established. PET/CT is not a substitute for high-quality contrast-enhanced CT, although it can be considered an adjunct to a formal pancreatic CT protocol in high-risk patients. Chest imaging to evaluate for the presence of pulmonary metastases is recommended as part of the preoperative workup for patients with no evidence of abdominal metastases on CT (see page 974).[43]

Patients with a mass in the pancreas on dynamic-phase spiral CT but no evidence of metastatic disease should also have a surgical consultation (see page 974). EUS may provide useful staging information in pancreatic cancer, particularly through assessment of certain types of vascular invasion.[44,45] EUS can also be used to evaluate periampullary masses, separating invasive from noninvasive lesions. In addition, EUS may have a role in better characterizing cystic pancreatic lesions. On EUS, malignant cystic lesions may present as a hypoechoic cystic/solid mass or as a complex cyst and are frequently associated with a dilated main pancreatic duct. Some therapeutic interventions can also be performed with EUS (e.g., celiac block, removal of ascites). The panel agreed that, although EUS has a high accuracy in assessing involvement of certain veins (e.g., portal vein), it is less accurate in imaging tumor invasion of the SMA.[45,46]

Patients without a mass in the pancreas on cross-sectional imaging and without evidence of metastatic disease should undergo additional imaging with EUS and/or endoscopic retrograde cholangiopancreatography (ERCP), as clinically indicated (see page 974). Distinguishing between benign and malignant strictures or stenosis can be difficult; however, severe stenosis and marked proximal dilatation more often indicate malignancy.[47] EUS is usually the preferred approach, with ERCP reserved for patients requiring biliary decompression. Stent placement at ERCP can be used to palliate biliary obstruction when surgery is not elected or must be delayed. MRI/magnetic resonance cholangiopancreatography (MRCP) is considered equivalent to EUS/ERCP in this setting. If studies are consistent with pancreatic cancer, then surgical consultation is recommended.

Restaging with high-quality abdominal and chest imaging is also recommended after surgery for resectable disease and before initiation of adjuvant therapy (see page 980). It should also be performed after administration of each treatment modality, when systemic gemcitabine is followed by chemoradiation in the adjuvant setting. In addition, this restaging is also recommended after administration of neoadjuvant therapy and before surgical resection for patients with borderline resectable disease (see pages 978 and 979).

Laparoscopy

Laparoscopy is another potentially valuable diagnostic tool for staging; it can identify peritoneal, capsular, or serosal implants or studding of metastatic tumor on the liver, which may be missed, even with the use of a pancreatic CT protocol.[48,49] The yield of laparoscopy depends on the quality of preoperative imaging and the likelihood of metastatic disease. A key goal is to avoid unnecessary laparotomy, although routine use of staging laparoscopy is controversial. The panel does not consider staging laparoscopy to be a substitute for poor-quality preoperative imaging.

Some recent evidence provides support for a selective approach to staging laparoscopy (i.e., it is performed if the presence of occult metastatic disease is suggested by high-quality imaging or certain clinical indicators).[50,51] For example, preoperative serum cancer antigen 19-9 (CA 19-9) levels greater than

100 U/mL have been associated with a greater likelihood of advanced disease and an increased probability of a positive finding on staging laparoscopy.[52] In a recent prospective review of 838 patients who were diagnosed with resectable pancreatic tumors on imaging evaluation between 1995 and 2005, 8% were found to have unresectable disease (12% yield if only pancreatic adenocarcinoma was considered) after subsequent laparoscopy performed at a single institution.[53] Characteristics associated with an increased laparoscopic yield include the tumor location, tumor histology, presence of weight loss and jaundice, and the facility conducting the imaging evaluation.

Diagnostic staging laparoscopy to rule out subradiologic metastases (especially for body and tail lesions) is used routinely in some NCCN institutions before surgery or chemoradiation, or selectively in patients who are at higher risk for disseminated disease (e.g., borderline resectable disease, markedly elevated CA 19-9, large primary tumors).The panel debated the value of a staging laparoscopy in patients with resectable/borderline resectable disease, and it is included as a category 2A recommendation for patients staged with resectable pancreatic cancer considered to be at increased risk of disseminated disease (see pages 976 and 985), and as a category 2B recommendation for patients with borderline resectable disease before and after administration of neoadjuvant therapy, because it is not uniformly performed at all NCCN institutions (see pages 977, 978, and 979). The panel considers positive cytology from washings obtained at laparoscopy or laparotomy to be equivalent to M1 disease.[54]

Tumor-Associated Antigens

Many tumor-associated antigens have been studied in connection with pancreatic adenocarcinoma, including carcinoembryonic antigen (CEA), pancreatic antioncofetal antigen, tissue polypeptide antigen, CA 125, and CA 19-9. A sialylated Lewis-a blood group antigen, CA 19-9 is commonly expressed and shed in pancreatic and hepatobiliary disease and many malignancies; thus, it is not tumor-specific. However, the degree of increase in CA 19-9 levels may be useful in differentiating pancreatic adenocarcinoma from inflammatory conditions of the pancreas,[55] and CA 19-9 tests may yield false-positive results in cases of benign biliary obstruction[56] or undetectable in Lewis-negative individuals.[57] Preoperative measurement of CA 19-9 levels should be performed after biliary decompression is complete (see page 975).

A low postoperative serum CA 19-9 level, and a decrease in serial CA 19-9 levels following surgery, have been found to correlate with survival for patients undergoing resection for pancreatic cancer.5[8–60] In one prospective study of patients undergoing surgery with curative intent, median survival for patients with postresectional CA 19-9 levels of less than 180 U/mL was significantly greater than for the group with higher CA 19-9 levels after surgery (HR, 3.53; $P < .0001$). Similarly, in a prospective study of patients with advanced pancreatic cancer, a dichotomized pretreatment CA 19-9 serum level was shown to be an independent prognostic factor for survival.[61] However, data are conflicting regarding the predictive significance of CA 19-9 response after chemotherapy in patients with advanced disease.[61–65] The panel recommends measuring serum CA 19-9 levels after surgery and before adjuvant therapy is administered (see page 980). Although no FDA-approved testing methodology exists for measuring serum CA 19-9 levels, several different methods are commercially available for quantifying this tumor-associated antigen. Serum CA 19-9 levels measured using one testing method cannot be extrapolated to results obtained using a different procedure.

Differential Diagnoses

Chronic pancreatitis and other benign conditions (e.g., autoimmune pancreatitis) are in the differential diagnosis of patients suspected of having pancreatic cancer.6[6–70]

Autoimmune pancreatitis, a rare form of chronic pancreatitis, is a heterogeneous disease that can present with clinical and radiologic characteristics of pancreatic cancer, such as jaundice, weight loss, an elevated CA 19-9 level, and the presence of diffuse pancreatic enlargement, a pancreatic ductal stricture, or a focal pancreatic mass.[71–73] A benign disease that can be effectively treated with corticosteroids, autoimmune pancreatitis must be distinguished from pancreatic cancer to avoid unnecessary surgery and prevent delay in the initiation of appropriate treatment.

Increased serum immunoglobulin (Ig) G levels supports a diagnosis of autoimmune pancreatitis, although an elevated serum IgG4 level is the most sensitive and specific laboratory indicator. The classic appearance of the pancreas on abdominal CT in patients with diffuse pancreatic involvement is a sausage-shaped enlargement of the organ surrounded

by a capsule-like peripheral rim, although focal enlargement of the pancreas is observed in some cases.[71] Cardinal histologic features of autoimmune pancreatitis include prominent lymphocytic infiltration of the pancreatic parenchyma with associated fibrosis.

Pathology

Biopsy: Although a histologic diagnosis is not required before surgery, it is necessary before administration of neoadjuvant therapy (see pages 977, 978, and 979), and for patients staged with locally advanced and unresectable pancreatic cancer or metastatic disease (see page 981). A histologic diagnosis of adenocarcinoma of the pancreas is often made using fine-needle aspiration (FNA) biopsy with either EUS-guidance (preferred) or CT (see page 977). EUS-directed FNA biopsy is preferable to CT-guided FNA in patients with resectable disease because of the much lower risk for peritoneal seeding with EUS-FNA compared with the percutaneous approach.[74] A negative biopsy should be confirmed by at least 1 repeat EUS biopsy (see pages 978 and 979). However, in some cases (e.g., borderline resectable disease), treatment (i.e., laparotomy) may still be recommended for these patients after 2 negative biopsies, especially if clinical and radiographic evidence strongly suggests pancreatic cancer (see pages 978 and 979).[33]

When clinical and imaging findings indicate that locally advanced disease is present, laparoscopy with biopsy can be considered if repeat FNA biopsy is negative (see page 981). In patients without obstructive jaundice at initial presentation, EUS-FNA is highly accurate and reliable for ruling in malignancy; in patients with obstructive jaundice and biliary stricture, EUS-FNA is less accurate.[30] Non-neoplastic and neoplastic cystic pancreatic lesions can be difficult to discriminate radiographically; however, EUS-guided FNA can be useful in the differential diagnosis of these lesions.[75] Pancreatic ductal brushings or biopsies can also be obtained at ERCP, often revealing malignant cytology consistent with pancreatic adenocarcinoma. It is important to reiterate that proof of malignancy through biopsy is not required before surgical resection and that a nondiagnostic biopsy should not delay surgical resection when the clinical suspicion for pancreatic cancer is high. The panel strongly recommends that all diagnostic and surgical management decisions involve multidisciplinary consultation.

Specimen Orientation, Pathologic Analysis, and Reporting: Pathology synoptic reports (protocols) are useful for reporting results from examinations of surgical specimens; these reports assist pathologists in providing clinically useful and relevant information. The panel supports pathology synoptic reports from the College of American Pathologists (CAP). The CAP protocol information can be accessed at http://www.cap.org/apps/docs/cancer_protocols/2005/pancreasexo05_ckw.doc.

On January 1, 2004, the Commission on Cancer (COC) of the American College of Surgeons mandated the use of specific checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. CAP protocols comply with COC requirements, and the latest revisions to the CAP pancreatic (exocrine) protocol were issued in January 2005. Pathologists should familiarize themselves with these documents.

The American Joint Committee on Cancer (AJCC) has developed staging criteria for adenocarcinoma of the pancreas (see the staging table, available online, in these guidelines, at www.NCCN.org [ST-1 and ST-2]).[76] Recent validation of concordance between AJCC stage and overall survival has been provided through evaluation of 121,713 patients with pancreatic adenocarcinoma in the National Cancer Database (NCDB).[77] Although the TNM staging criteria for pancreatic cancer in the 7th edition of the *AJCC Cancer Staging Manual* have taken into account the fact that tumors of the pancreas are evaluated preoperatively by CT to determine resectability status, these staging criteria also include information that can be determined only through postsurgical pathologic evaluation of resected tumor.[76] For clinical purposes, most NCCN Member Institutions use a clinical staging system based mainly on results of presurgical imaging studies. After staging with CT (and EUS/ERCP in some cases), preoperative CA 19-9 testing, and evaluation for the presence of jaundice, disease is classified as 1) resectable, 2) borderline resectable (i.e., tumors involved with nearby structures which renders them neither clearly resectable nor clearly unresectable), 3) locally advanced unresectable (i.e., tumors involved with nearby structures to an extent that renders them unresectable despite the absence of evidence of metastatic disease), or 4) disseminated (see Criteria for Resec-

tion, below), and this is the system used throughout the guidelines. Although not part of the TNM staging system criteria, the AJCC recommends that surgeons score the completeness of the resection as 1) R0 for complete tumor resection with all margins negative, 2) R1 for incomplete tumor resection with microscopic involvement of a margin, or 3) R2 for incomplete tumor resection with gross residual tumor that was not resected.[76]

Wide variation exists in the reported R1 rates of pancreaticoduodenectomy specimens.[78] Clear definitions of microscopic margin involvement and a circumferential resection margin are needed. Although several methods of specimen orientation and pathologic analysis have been described, no uniform consensus exists on a standardized protocol for the pathologic examination of these specimens.[78–80]

A pathologic evaluation of the surgical specimen involves both the pathologist and surgeon.[78,80] For example, to evaluate resection margin status, surgical margins must be inked appropriately and the surgeon must specify whether a complete resection was performed to enable the pathologist to distinguish between R1 and R2 resections.[81]

Surgical Management

Criteria for Resection

Clearly, surgical resection is the only potentially curative technique for managing pancreatic cancer. However, more than 80% of patients present with disease that cannot be cured with surgical resection.[82] Early concerns about high mortality associated with various pancreatic resection procedures[83] have now been lessened by studies showing an acceptably low (< 5%) mortality in experienced centers (see later discussion).[84] Even under the most optimal conditions, however, the median survival of resected patients ranges from 15 to 19 months, and the 5-year survival rate is approximately 20%.[85] Negative margin status (i.e., R0 resection), tumor DNA content, tumor size, and absence of lymph node metastases are the strongest prognostic indicators for long-term patient survival.[86–88] Regarding margin status, evidence exists for the converse statement: survival benefits of an R1 resection may be comparable to palliative chemoradiation without surgery.[89]

The panel recommends that decisions about diagnostic management and resectability always involve multidisciplinary consultation, with appropriate radiographic studies to evaluate the extent of disease. Although patients with visceral, peritoneal, and pleural metastases, and metastases to nodes beyond the field of resection clearly derive no benefit from resection, institutions seem to differ in their approaches to patients with locoregional (pancreas and peripancreatic lymph node) disease involvement. Based on their clinical experience with the primary management of pancreatic tumors, an expert consensus group developed criteria to define tumor resectability to improve patient selection for surgery and increase the likelihood of an R0 resection.[33] Using these criteria, tumors are classified as resectable, borderline resectable, or unresectable (e.g., locally advanced or metastatic disease; see page 986).

The absence of evidence for peritoneal or hepatic metastases after a thorough radiographic assessment is a criterion for both resectable and borderline resectable disease. Radiographic findings of tumor abutment on the portal vein or SMV with or without venous deformity, and limited encasement of the mesenteric and portal vein (i.e., short segment occlusion with suitable vessel for anastomosis above and below) represent the extent of venous involvement that would categorize a tumor as borderline resectable. Radiographic findings that suggest borderline arterial involvement include encasement of a short segment of the hepatic artery without evidence of tumor extension to the celiac axis and/or tumor abutment of the SMA involving 180° or less of the artery circumference. Patients with resectable disease have clear fat planes around the celiac axis, hepatic artery, and SMA and no radiographic evidence of SMV and portal vein abutment, distortion, tumor thrombus, or venous encasement.[33]

The likelihood of attaining negative surgical margins (i.e., R0 resection) is a key criterion to consider when determining whether a patient is a potential candidate for resection.[90,91] In this context, a borderline resectable lesion can be defined as one that has a higher likelihood of an incomplete (R1 or R2) resection (see page 986).

Primary Surgery for Pancreatic Cancer

The nature and extent of the surgery for resectable tumors depend on the location and size of the tumor.

Because tumors of the body and tail cause symptoms late in their development, they are usually advanced at diagnosis and uncommonly resectable. Pa-

tients with tumors in the head of the pancreas, who usually present because of jaundice, are treated with pancreaticoduodenectomy. A review of the biomedical literature indicates that no universally accepted surgical techniques exist for performing this procedure. This complex procedure has several controversial issues associated with it that are discussed in more detail in the following sections. Nevertheless, surgery should be performed only by surgeons capable of managing tumor–vessel involvement.

Preoperative Biliary Drainage

The main goals of preoperative biliary drainage are to alleviate the symptoms of pruritus and cholangitis and to potentially make surgery less morbid through improving liver function preoperatively. Although controversial, several studies have suggested that pancreaticoduodenectomy is associated with higher perioperative mortality when performed in the setting of hyperbilirubinemia.[92–94] Stenting of the biliary system can improve symptoms and liver function, but whether these changes can decrease the mortality rate of the Whipple procedure is unclear. Several prospective and retrospective studies have failed to show decreased mortality in patients with preoperative biliary drainage.[95–101] In 1999, a retrospective study from Memorial Sloan-Kettering Cancer Center (MSKCC) examined 240 consecutive pancreaticoduodenectomies in which 53% of patients underwent preoperative biliary decompression.[102] This study found a statistical relationship between the use of preoperative drainage (irrespective of the method used) and increased postoperative complications, including death, in patients who went straight to surgery.

In contrast, the University of Texas MD Anderson Cancer Center (MDACC) reported on their experience with more than 300 patients, of whom 57% had preoperative biliary drainage,[103] as part of a neoadjuvant chemoradiation program. Wound complications were significantly increased in the drainage group; however, no other association was found for sepsis, fistulae, or death. In addition, a recent multicenter, randomized trial comparing preoperative biliary drainage with surgery alone for 202 patients with cancer of the pancreatic head characterized by obstructive jaundice showed a nearly 2-fold increase in the rate of serious complications in the former group (74% vs. 39%; relative risk in the early-surgery group, 0.54; 95% CI, 0.41–0.71; $P < .001$), although no significant differences in surgery-related complications, length of hospital stay, or mortality were observed.[104] Based on these reports, most groups who perform resection first advocate selective use of decompression only in patients who are symptomatic or septic, or for whom surgical resection is significantly delayed. For patients with jaundice undergoing neoadjuvant induction therapy before pancreatic resection, biliary decompression is necessary to initiate therapy and seems to be well tolerated, with minimal increase in perioperative morbidity.

Patients who present with jaundice and potentially resectable disease may require placement of a temporary stent (e.g., plastic stent) along with antibiotic coverage if symptoms of cholangitis or fever are present (see page 985). Endoscopic placement of a temporary stent and normalization of bilirubin levels is recommended before CA 19-9 testing during the initial workup of patients with obstructed jaundice characterized by symptoms of cholangitis or fever when no evidence of metastatic disease is present (see page 975). Stent placement is also recommended before neoadjuvant therapy is administered for patients with jaundice and borderline resectable disease that is biopsy-positive (see page 979).

Pylorus Preservation

Reconstruction options for the stomach after pancreaticoduodenectomy center around preservation of the pylorus. Traverso and Longmire[105] reported the modern use of pylorus preservation in 1978. The hypothesis was that preservation would improve emptying and provide nutritional benefit, but the benefits have been inconsistent. Yeo et al.[106] reported no adverse affects of pylorus preservation; however, van Berge Henegouwen et al.[107] reported longer nasogastric drainage times. In several randomized and nonrandomized studies,[108–112] the pylorus-preserving procedure seemed to be associated with shorter surgical duration. No consistent data suggest that pylorus preservation leads to a better quality of life or nutritional status in patients after resection. Thus, pylorus-preserving pancreaticoduodenectomy remains an unproven but certainly acceptable alternative to classic pancreaticoduodenectomy performed with antrectomy.

Pancreatic Anastomosis

Efforts in this area have focused on preventing pancreatic leaks and fistulas, which are morbid and po-

tentially lethal complications of pancreaticoduodenectomy. Pancreaticojejunostomy has traditionally been the standard reconstruction and is the major focus of morbidity and mortality after pancreaticoduodenectomy because of leaks, abscess formation, and fistulas from this anastomosis. A randomized study at Johns Hopkins Hospital found no difference in fistula rates after pancreaticojejunostomy and pancreaticogastrostomy.[113] Furthermore, surgeons have examined various other options for the pancreaticojejunal anastomosis; end-to-end, end-to-side, duct-to-mucosa, and invaginating techniques have all proven to be safe and effective.[114,115] Results of a prospective trial show that pancreatic fistula can be almost entirely avoided with a technique that combines placement/tying of sutures under magnification with meticulous attention to blood supply.[116] Stents used in the 1930s and 1940s continue to be used today, but no data suggest that they decrease leak rates.[117] Pancreatic fistula rates are similar (ranging in most studies from 6%–16%),[106,114,118] although the exact way to define a pancreatic leak in terms of volume and duration of drainage remains controversial.[119]

In addition to technical modifications, octreotide has been examined for its ability to decrease postoperative pancreaticojejunal leaks in patients undergoing pancreatic resections. However, octreotide did not decrease fistula rates when assessed in 2 prospective, randomized, double-blind, placebo-controlled studies (from MDACC and Johns Hopkins Hospital).[120,121] Finally, the use of fibrin glue sealant does not seem to decrease the rate of pancreatic fistulas.[122]

Portal Vein Resection

Vascular invasion has been a conventional contraindication to pancreatic resection. Early attempts at resection and reconstruction of the SMA and SMV in the 1970s were associated with poor results in a few patients who underwent "regional" pancreatectomy.[123] Both autologous and synthetic grafts were used for arterial and venous reconstructions. As morbidity from pancreaticoduodenectomy decreased, a subset of patients was identified who were in need of resection of the SMV wall to achieve negative margins during removal of their tumors. Thus, the 1990s saw a renewed interest in vein resection for complete resections. The group from MDACC championed this approach, arguing that because overall mortality from pancreaticoduodenectomy has decreased, vein resection and reconstruction allow for complete resection and are not associated with increased morbidity or mortality compared with patients who did not require vein resection.[124] Furthermore, long-term outcome is not significantly worse.[125] Although compelling, this approach has not been universally accepted. During the 1990s, several studies reported operative mortality of 0% to 16.5%, 3-year Kaplan-Meier survival of 12% to 23%, and median survival of 5 to 14 months in patients undergoing vein resection.[126–129] A recent study found that properly selected patients (n = 141) with adenocarcinoma of the pancreatic head who required vein resection had a median survival of approximately 2 years, which did not differ from that for those undergoing standard pancreaticoduodenectomy and was superior to historical patients believed to have locally advanced disease who did not undergo surgical treatment.[130] Thus, a few groups have recommended caution and only use vein resection for selected patients.

Extended Lymphadenectomy

The role of lymph node dissection as a component of pancreaticoduodenectomy has remained controversial during the past several decades. In patients who undergo pancreaticoduodenectomy, decreased survival led to a hypothesis that a more aggressive lymphadenectomy might improve survival. In the 1970s and 1980s, pathology and autopsy studies showed a high incidence of nodal metastasis (sometimes as high as 80%), leading some groups to propose a more aggressive lymphadenectomy[131,132] to regionally control disease. The definition varies regarding what a regional or extended lymphadenectomy entails in patients undergoing pancreaticoduodenectomy. However, this procedure is most commonly performed in the United States by removing not only the peripancreatic lymph nodes, but also the soft tissue in the retroperitoneum from the hilum of the right kidney to the left lateral border of the aorta in one axis, and from the portal vein to the origin of the inferior mesenteric artery in the other.[133]

Several retrospective or single-institution nonrandomized studies have examined the role of extended lymphadenectomy. The most promising results are from Japan, with a few studies reporting improved survival in patients who underwent more extensive operations, including lymphadenectomy, although these studies included only a few patients.[134,135] In general, these studies had significant

imbalances among patients with regard to disease stage. In contrast, several additional studies from the United States and Europe have failed to show a survival advantage in patients undergoing regional lymphadenectomy.[136,137]

Two prospective randomized trials have tried to address the role of lymphadenectomy in patients undergoing pancreaticoduodenectomy. The Italian Multicenter Lymphadenectomy Group reported on a series of 81 patients randomly assigned to pancreaticoduodenectomy with or without extended lymph node resection. Although the statistical power was low, this study did not support the concept that an extended lymphadenectomy is a good prognostic factor.[138] A larger randomized prospective trial is currently being performed at Johns Hopkins Hospital to evaluate the role of extended lymph node dissections.[139] At last update, 299 patients were entered and no difference had been detected in operative mortality between treatment groups. The group of patients who received the regional lymphadenectomy in addition to pancreaticoduodenectomy had longer operation times, but overall median survival did not differ between the groups at 1, 3, and 5 years.[140]

Current information does not show any survival advantage to performing a regional lymphadenectomy in addition to the standard pancreaticoduodenectomy. Thus, a regional lymphadenectomy should not be considered a routine part of the Whipple procedure. Outside the setting of a clinical trial, the extended node dissection should be reserved for patients with larger tumors or for reoperative patients in whom removing the retroperitoneal nodal tissue can allow dissection in a virgin plane and possibly provide a higher chance of a margin-negative resection. Currently, data suggest that nodal metastases are a marker of systemic disease and that their removal is unlikely to alter overall survival.

Effect of Clinical Volume

Several studies have examined the effect of institutional volume on patient outcomes. The fundamental premise was that the decreasing morbidity and mortality seen in the 1980s and 1990s were the direct result of large single-institution experiences. Moreover, the concern was that if surgeons performed pancreaticoduodenectomy less frequently, patients might have increased morbidity and mortality. In 1993, Edge et al.[141] assessed 223 pancreaticoduodenectomies from 26 United States hospitals, but found that caseload did not correlate with mortality. However, surgeons who performed fewer than 4 resections per year had more complications. The group from MSKCC examined the issue in 1995 and found that in a cohort of 1972 patients, high-volume centers in New York state had significantly less mortality (4% vs. 12.3%) than low-volume centers.[142] High volume was defined as more than 40 cases per year, and this relationship correlated in a regression analysis. Notably, 75% of the cases in New York were performed in low-volume centers. Furthermore, regional outcomes with pancreaticoduodenectomy from United States hospitals were assessed in several other studies that have also reported decreased mortality, hospital length of stay, and overall cost at higher-volume centers compared with low-volume centers.[143–147] Interestingly, this effect was also seen in reports from Canada and the Netherlands.[148,149]

The definitions of high and low volume varied among all these studies. However, a striking difference is seen when the mortality rates from pancreaticoduodenectomy in very–low-volume (0–1 procedure per year) and low-volume (1–2 procedures per year) hospitals are compared with rates in higher-volume hospitals (> 5 procedures per year).[150] In-hospital mortality rates at these very–low-volume and low-volume hospitals were significantly higher than at high-volume hospitals (16% and 12%, respectively, vs. 4%; $P < .001$). The importance of hospital volume in improving survival after pancreatic cancer surgery is even more marked when pancreaticoduodenectomy is compared with other major surgeries. In a retrospective analysis of data from the national Medicare claims database and the Nationwide Inpatient Sample, hospitals performing 6 to 16 and more than 16 procedures per year were classified as "high-" and "very–high-" volume centers, respectively.[151] In this study, 6 or more pancreatic resections were performed at only 6.3% of hospitals. The largest difference in operative mortality between very–low-volume (17.6%) and high-volume (3.8%) centers is seen for pancreaticoduodenectomy compared with major surgery at any other sites, further reinforcing the magnitude of the effect that high-volume centers can specifically have on pancreatic cancer outcomes. The panel recommends that pancreatic resections be performed at institutions that perform a large number (> 15–20) of pancreatic resections annually (see page 985).

A recent study involving 301,033 patients with

pancreatic adenocarcinoma included in the NCDB evaluated the treatment patterns of 1667 hospitals over a 19-year period.[152] During that time, the pancreatectomy rate and use of multimodality adjuvant therapy (i.e., surgery plus chemoradiation) for patients with stage I and II disease increased significantly (pancreatectomy rate increased from 39.6% to 49.3%; $P < .001$; use of multimodality therapy increased from 26.8% to 38.7%; $P < .001$). Furthermore, patients were more likely to undergo these treatments at academic institutions, particularly those considered to be high-volume hospitals. However, an analysis of 9559 patients diagnosed with early-stage disease from 1995 to 2004 showed that a high percentage (38.2%) of these patients with potentially resectable disease were not treated surgically.[153] Nevertheless, panel consensus is that patients should be selected for surgery based on curative intent as determined by the probability of obtaining R0 resection margins. Patients at high risk for positive surgical margins are not considered good candidates for an up-front resection.

Adjuvant Therapy

Postoperative Therapy

In 1985, the Gastrointestinal Tumor Study Group (GITSG) initially reported that the median survival of patients undergoing pancreaticoduodenectomy could be prolonged almost twofold by postoperative chemoradiation.[154] In this study, patients were randomized to either observation or radiation therapy (RT) combined with an intermittent bolus of 5-fluorouracil (5-FU) after resection. A standard split course of 4000 cGy was used. 5-FU, 500 mg/m^2 daily for 3 days, was given concurrently with each 2000-cGy segment of RT. The 5-FU regimen was then continued weekly for a full 2 years. In addition to a prolonged median survival, chemoradiation also resulted in a 2-year actuarial survival of 43%, compared with 18% in the control group.

In a phase III trial (40891) assessing adjuvant radiotherapy and 5-FU versus observation alone after surgery in patients with both ampullary and pancreatic adenocarcinoma the EORTC found the benefit of therapy was small in a subset of patients with pancreatic adenocarcinoma and was not statistically significant.[155] At a median follow-up of 11.7 years, no statistically significant differences were observed between the study arms with respect to progression-free or overall survival for the subset of patients with pancreatic cancer.[156]

Provocative but controversial results from the European Study Group for Pancreatic Cancer (ESPAC)-1 trial have been reported by Neoptolemos et al.[157] Results of this study suggest that 5-FU/leucovorin is superior to observation and that chemoradiation is unnecessary and perhaps harmful. However, the ESPAC-1 trial has been criticized for serious flaws in conduct and reporting, and for lack of attention to quality control for RT.[158,159] Therefore, these latest results do not eliminate 5-FU–based chemoradiation as an acceptable choice in the adjuvant setting.

An intention to treat analysis of data from the large phase III CONKO-001 trial, which randomized 368 patients without prior chemotherapy or RT to adjuvant gemcitabine versus observation after macroscopically complete resection, showed that the primary end point of increased disease-free survival was met (median disease-free survival, 13.4 vs. 6.9 months; $P < .001$, log rank).[160] Recently, final results from this study showed median overall survival to be improved significantly for patients in the gemcitabine arm (22.8 vs. 20.2 months; $P = .005$).[161] Significant differences in median overall survival only became apparent at 2 years, with an absolute survival difference of 12.0% observed between the groups at 5 years (21% vs. 5%).

The phase II study by the Radiation Therapy Oncology Group (RTOG 97-04) evaluated pre- (3 weeks duration) and postchemoradiation 5-FU (3 months duration) versus pre- and postchemoradiation gemcitabine for postoperative adjuvant treatment of resected pancreatic adenocarcinoma.[162] This trial, which used daily fractionated RT, included prospective quality assurance of all patients and central review of preoperative CT imaging and radiation fields.[163] For patients with tumors of the pancreas head, representing 388 of the 451 patients enrolled in the trial, results showed a nonstatistically significant increase in overall survival in the gemcitabine arm compared with the 5-FU arm (median survival and 3-year survival rate of 20.5 months and 31%, respectively, vs. 16.9 months and 22%, respectively; $P = .09$); this benefit became more pronounced on multivariate analysis. Although results from RTOG 97-04 suggest a possible advantage for adjuvant therapy with gemcitabine over infusional 5-FU, re-

sults from the prospective randomized trial of bolus 5-FU/leucovorin versus gemcitabine after surgery (ESPAC-3) showed no difference in overall survival when the groups receiving adjuvant 5-FU/leucovorin and adjuvant gemcitabine were compared (median survival, 23.0 and 23.6 months, respectively).[164]

Results of RTOG 97-04 cannot be directly compared with the results of the CONKO-001, ESPAC-1, or ESPAC-3 trials because of differences in treatment design and fundamental differences in patient characteristics (e.g., patients enrolled in CONKO-001 were more likely to have negative lymph node status and positive resection margins than those in RTOG 97-04). In addition, limitations of some of these trials include problems with surgery and pathology quality control, and inconsistencies in postoperative restaging with CT.[165] However, median overall survival is remarkably similar among patients in the gemcitabine arm of CONKO-001 (22.8 months), gemcitabine-containing arm of RTOG 9704 (20.5 months), bolus 5-FU/leucovorin arm of ESPAC-1 (20.1 months), and gemcitabine and 5-FU/leucovorin arms of the ESPAC-3 study (23.6 and 23.0 months). Therefore, no definite standard has been established in the adjuvant treatment of pancreatic cancer, and both 5-FU–based chemoradiation with additional gemcitabine-chemotherapy and chemotherapy alone with gemcitabine, 5-FU/leucovorin, or capecitabine are listed in the guidelines as options for adjuvant treatment. All of these adjuvant therapy options are designated as category 2A recommendations, with the exception of capecitabine (category 2B). However, panel consensus was that when chemotherapy alone is chosen as adjuvant therapy, gemcitabine is preferred over either 5-FU/leucovorin or capecitabine for most patients because of its more favorable toxicity profile, and that when chemoradiation is chosen, systemic gemcitabine should be administered before 5-FU–based chemoradiation.

Although the optimal combination and sequencing of RT has yet to be defined, the panel recommends that when postoperative RT is given, it should be administered at a dose of 45 to 54 Gy (1.8–2.0 Gy/d; see page 988).[166] Use of CT simulation and 3-dimensional treatment planning is strongly encouraged. Treatment volumes should be based on preoperative CT scans and surgical clips (when placed). Treatment volumes include the location of the primary tumor and regional lymph nodes. Radiation is usually given in combination with continuous infusion 5-FU or capecitabine; the panel recommends that 5-FU–based chemoradiation be delivered after systemic gemcitabine in the adjuvant setting (see page 980), because emerging data in the study of locally advanced disease suggest that a period of chemotherapy followed by consolidated chemoradiation may be preferable to up-front chemoradiation.[167–169] Therefore, the panel recommends that when chemoradiation is considered as adjuvant therapy, it should be administered after an adequate course (i.e., up to 4 months) of systemic chemotherapy.

Adjuvant chemotherapy or chemoradiation should only be considered for patients who have adequately recovered from surgery; treatment should ideally be initiated within 4 to 8 weeks (see page 980). After surgery, the panel recommends that patients undergo a pretreatment baseline assessment, including CT scan and CA 19-9 level, to evaluate for the presence of metastatic disease before adjuvant chemoradiation is initiated. Furthermore, the panel recommends restaging patients with a CT scan after systemic chemotherapy if it will precede chemoradiation (see page 980). Adjuvant therapy is not restricted to patients who have not had neoadjuvant therapy, but adjuvant chemoradiation cannot be administered to patients who have undergone neoadjuvant chemoradiation.

Preoperative (Neoadjuvant) Therapy

Novel contemporary approaches to adjuvant therapy have focused on preoperative (neoadjuvant) therapy with the goal of improving overall survival.[170,171] Although not widely investigated, several studies have evaluated the use of neoadjuvant chemoradiation in patients with resectable disease.[37,38,172–174] However, no randomized trials have addressed this issue. A retrospective review of the collective experience at MDACC indicated that the use of preoperative chemoradiation therapy in patients with resectable disease does not seem to be clearly disadvantageous, and that more patients may benefit if the therapy is given preoperatively because the prolonged recovery after pancreaticoduodenectomy prevents the delivery of postoperative therapy in up to 25% of eligible patients.[173]

Other putative advantages to administering neoadjuvant therapy include the potential to select for surgery the patients with more stable disease or disease that is more responsive to therapy; treatment of tissue that has not been subjected to surgery and,

hence, may be more sensitive to chemoradiation; treatment of micrometastases at a earlier stage; and the potential to downsize tumors to increase the likelihood of a margin-free resection.[90,170,175] In an analysis of 132 consecutive patients, the MDACC group reported that combined preoperative chemoradiation and pancreaticoduodenectomy yielded a median survival of 21 months, and 31% of patients were alive without evidence of disease.[173]

Some studies have addressed the use of preoperative chemoradiation to convert selected patients with unresectable disease to a resectable status.[171,172,175–180] Although emerging evidence suggests that preoperative therapy provides a better chance of margin-negative resection,[181] results of randomized trials involving a clinical end point of R0 resection rate have not been reported. Furthermore, the optimal neoadjuvant regimen has not been established.

Although most studies investigating the neoadjuvant experience in patients with pancreatic cancer are retrospective, several small phase II studies have been recently published. In a randomized phase II trial evaluating the safety and efficacy of gemcitabine-based chemotherapy regimens as neoadjuvant therapy for patients with potentially resectable pancreatic cancer, more patients undergoing combination therapy were able to undergo resection than those receiving gemcitabine alone.[182]

In another prospective trial, preoperative radiation with concurrent gemcitabine was administered to 86 patients with potentially resectable disease, and patients were restaged 4 to 6 weeks after completion of neoadjuvant treatment.[183] Although all patients were able to complete neoadjuvant therapy, only 64 were able to undergo surgery at restaging; most of the remaining patients were precluded from undergoing a pancreaticoduodenectomy because of the presence of more advanced disease. Similar results were observed in another phase II trial involving preoperative gemcitabine/cisplatin followed by gemcitabine-based chemoradiation, although of the 90 patients enrolled, only 79 were able to complete neoadjuvant therapy and 52 underwent surgery.[184] Again, the main reason patients were precluded from surgery was the finding of more advanced disease at restaging after completion of neoadjuvant therapy. A cross-study comparison of these results suggests that inclusion of preoperative chemotherapy before initiation of gemcitabine-based chemoradiation did not improve survival. These results provide support for restaging patients with abdominal and chest imaging and diagnostic laparoscopy before committing them to laparotomy after neoadjuvant therapy.

Most member institutions prefer an initial approach involving neoadjuvant therapy as opposed to immediate surgery for patients with borderline resectable disease, and the panel recommends neoadjuvant therapy as an alternative to up-front resection after disease is clinically staged as borderline resectable (see page 977). Because most but not all NCCN centers administer neoadjuvant therapy to patients with borderline resectable disease, both of these options are designated as category 2B recommendations. EUS-directed biopsy is the preferred method of obtaining histologic confirmation of disease in these patients, and this confirmation is necessary before administering neoadjuvant therapy. A repeat biopsy should be performed when initial biopsy results are negative. In addition, staging laparoscopy, performed to evaluate for the possible presence of metastatic disease, is also recommended (category 2B) before and after neoadjuvant therapy (see pages 977, 978, and 979). Placement of a stent is recommended before initiation of neoadjuvant therapy in patients with jaundice (see page 979). Neoadjuvant therapy regimens are often similar to those used to treat locally advanced disease (see Chemoradiation for Locally Advanced Disease, below). Abdominal and chest imaging should be repeated after neoadjuvant therapy.

The panel also recommends that neoadjuvant therapy in the context of a clinical trial be considered for patients clinically staged as having resectable disease (see page 976). However, the panel does not support the use of neoadjuvant therapy outside of a clinical trial for patients clinically staged with resectable disease.

Chemoradiation for Locally Advanced Disease

Chemoradiation is a conventional option for the management of unresectable locoregional pancreatic cancer (see pages 981, 982, and 988), although the efficacy of chemoradiation in this population of patients is controversial.[185] The role of chemoradiation was initially defined in a trial conducted by GITSG.[186] This study compared bolus 5-FU and split-course radiation (total dose, 4000 cGy) with

radiation alone or with 6000 cGy combined with 5-FU. A nearly twofold increase in median survival (42.2 vs. 22.9 weeks) was observed in the bolus 5-FU and 4000 cGy arm compared with radiation alone. Subsequent generations of studies have sought to optimize the use of 5-FU, and most contemporary studies no longer use split-course radiation.

For primary definitive chemoradiation therapy, NCCN recommends doses of 50 to 60 Gy (1.8–2.0 Gy/d) with concomitant 5-FU (see page 988).[166,187] Use of CT simulation and 3-dimensional treatment planning is strongly encouraged. Treatment volumes should be based on CT scans and surgical clips (when placed). Radiation is usually given in combination with 5-FU. When 5-FU–based chemoradiation is used, treatment volumes include the location of the primary tumor and regional lymph nodes. Currently, systemic chemotherapy followed by chemoradiation therapy is recommended for patients with unresectable disease, no metastases, and good performance status.

Gemcitabine has also been used as a radiation sensitizer.[183,184,188–190] Evidence suggests that concurrent gemcitabine and radiation can yield similar outcomes compared with 5-FU–based chemoradiation,[190,191] although no randomized trials have directly assessed whether any of these modifications are superior to the original trial results reported by GITSG. Results from a recent phase II study of patients with locally advanced pancreatic adenocarcinoma from the North Central Cancer Treatment Group evaluated the safety and efficacy of RT in combination with gemcitabine and cisplatin. Although this regimen had acceptable toxicity, no survival benefit over other regimens was observed.[192] Chemoradiation is included in the guidelines as an option for patients with locally advanced unresectable disease with no metastases who have a good performance status (category 2A; see pages 981 and 982). The panel recommends that an adequate course (i.e., up to 4 months) of initial systemic chemotherapy (gemcitabine-based) be administered to patients with locally advanced disease for whom chemoradiation therapy is planned, because emerging data suggest that a period of chemotherapy followed by consolidated chemoradiation may be preferable to up-front chemoradiation.[167–169,193] A treatment approach using an initial 3- to 4-month course of chemotherapy may facilitate systemic disease control while simultaneously helping to uncover whether the disease is rapidly progressive. For example, a retrospective analysis of outcomes from the Oncology Multidisciplinary Research Group (GERCOR) studies indicated that first-line treatment with chemotherapy may be a useful strategy for selecting patients with locally advanced disease who are more likely to benefit from subsequent chemoradiation therapy.[167] This approach is currently being evaluated in an ongoing phase III trial (GERCOR-LAP-07-D07-1). When systemic chemotherapy precedes administration of chemoradiation, the panel recommends restaging with a CT scan before RT.

Chemotherapy without RT is also an option for patients with locally advanced pancreatic cancer, especially for those with poor performance status (see pages 981, 982, and 989). Results of 2 early randomized trials comparing chemoradiation with chemotherapy in locally advanced disease were contradictory.[194,195] A phase III randomized trial (ECOG-4201) comparing gemcitabine with gemcitabine plus RT followed by gemcitabine alone in patients with locally advanced, unresectable pancreatic cancer was closed early because of poor accrual. However, an intent-to-treat analysis of data for the 74 patients enrolled showed that median overall survival was significantly longer in the chemoradiation therapy arm of the study (11.0 vs. 9.2 months; $P = .034$).[196]

The benefit of chemotherapy versus chemoradiation was also addressed in the phase III FFCD-SFRO study from France in which patients with locally advanced pancreatic cancer were randomly assigned to receive either gemcitabine alone or an intensive induction regimen of chemoradiation with 5-FU plus cisplatin followed by gemcitabine maintenance treatment.[197] In this study, gemcitabine alone was associated with a significantly increased overall survival rate at 1 year compared with chemoradiation (53% vs. 32%). Although this study was stopped before the planned inclusion, patients in the chemoradiation arm experienced increased toxicity and were more likely to undergo a shorter course of maintenance therapy with gemcitabine, raising the question of whether the observed differences in survival were more likely attributable to the toxicity of the chemoradiation regimen than the efficacy of the gemcitabine chemotherapy regimen.

Chemotherapy for Advanced Disease

General Principles

Systemic therapy is used in the adjuvant setting and in the management of locally advanced unresectable and metastatic disease. The primary goals of treatment for advanced pancreatic cancer are palliation and improved survival. Although some effect on survival may be achieved, these benefits are usually limited to patients with an adequate performance status (ECOG 0–2). Patients who present with very poor performance status may benefit from the administration of gemcitabine, but comfort-directed measures are always paramount (see NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] on Supportive Care; to view the index of supportive care guidelines, visit the NCCN Web site at www.NCCN.org). Before initiating cytotoxic therapy, an open dialogue regarding the goals of treatment should occur, and adjunctive strategies should be discussed (including nonsurgical bypass and celiac block for pain; see Palliation of Locally Advanced and Metastatic Disease, page 1006, and page 987). Notably, debilitated patients with advanced disease may have abrupt changes in clinical status. Therefore, if treatment is begun, it should proceed with close follow-up. Patients may experience sudden onset of bleeding or thromboembolism, rapidly escalating pain, biliary stent occlusion, cholangitis, or other infections. Moreover, clinically meaningful tumor progression may develop quickly, and tumor-related symptoms may be inappropriately attributed to chemotherapy or other causes. For instance, patients who complain of intractable nausea and vomiting may have gastric outlet obstruction rather than chemotherapy-induced emesis. Peritoneal carcinomatosis may manifest as ascites or, in its more subtle form, as abdominal bloating, decreased oral intake, and constipation.

Role of Gemcitabine

For patients with locally advanced or metastatic disease, gemcitabine has been established as providing clinical benefit and a modest survival advantage over treatment with bolus 5-FU.[198] The panel recommends gemcitabine monotherapy (1000 mg/m^2 over 30 minutes, weekly for 3 weeks every 28 days) as standard front-line therapy for patients with metastatic disease (category 1; see pages 983 and 989).[198] The panel also debated whether gemcitabine monotherapy should be recommended for patients with unresectable, locoregional disease and a poor performance status. Because the approved indications for gemcitabine include symptom relief, the panel recommends gemcitabine as a reasonable option for symptomatic patients (category 1 for patients with poor performance status; category 2A for patients with good performance status). Other options for selected patients include gemcitabine-based combination therapy (category 2A; see Gemcitabine Combinations, below) or best supportive care (see NCCN Guidelines on Supportive Care [to view the index of supportive care guidelines, visit www.NCCN.org] and pages 981 and 982). For patients who derive clinical benefit from initial gemcitabine treatment in the setting of locally advanced disease, without developing distant disease, subsequent chemoradiation may enhance local control. After disease progression, fluorinated pyrimidine-based therapy is an option for some patients (see Second-Line Therapy, page 1005).

Fixed-Dose Rate Gemcitabine: Recent studies have suggested that the infusion rate of gemcitabine may be important for its efficacy. Gemcitabine is a prodrug, which must be phosphorylated for antitumor activity. Clinical studies have shown that administering gemcitabine at a fixed-dose rate ([FDR] 10 mg/m^2/min) maximizes intracellular concentrations of the phosphorylated forms of gemcitabine.[199] In a randomized phase II trial, the infusion of gemcitabine at an FDR led to a higher response rate and better survival compared with gemcitabine delivered at a higher dose over 30 minutes.[200] In the phase III randomized ECOG 6201 trial of patients with advanced pancreatic cancer, median survival was increased in the group receiving FDR gemcitabine compared with those receiving standard gemcitabine (6.2 vs. 4.9 months; $P = .04$), although this outcome did not satisfy the protocol-specified criteria for superiority.[201] When gemcitabine is considered for the treatment of advanced pancreatic cancer, the panel views FDR gemcitabine (10 mg/m^2/min) as a reasonable alternative to the standard infusion of gemcitabine over 30 minutes (category 2B). FDR gemcitabine is incorporated into some commonly used gemcitabine-based regimens (e.g., GEMOX [gemcitabine, oxaliplatin], GTX [gemcitabine, docetaxel, capecitabine]).[202,203]

Gemcitabine Combinations: The panel also acknowledged that, historically, combination chemotherapy has not appeared to be superior to mono-

therapy in the era of 5-FU–based therapy. However, because gemcitabine is superior to bolus 5-FU when efficacy end points of survival and relief from symptoms are used, it is now often combined with other chemotherapeutic agents for patients with good performance status. Gemcitabine has been investigated in combination with potentially synergistic agents (e.g., cisplatin, oxaliplatin, capecitabine, 5-FU, and irinotecan) or in a multidrug combination (e.g., cisplatin, epirubicin, gemcitabine, and 5-FU).[201–215]

Data on the survival impact of combining gemcitabine with a platinum agent are conflicting, and results of randomized controlled trials do not support the use of gemcitabine plus cisplatin for treating advanced pancreatic cancer. Three phase III trials evaluating the combination of gemcitabine with cisplatin versus gemcitabine alone in patients with advanced pancreatic cancer failed to show a significant survival benefit for the combination regimen compared with the single agent.[205,208,214] Similarly, no survival benefit was observed in a phase III trial investigating GEMOX compared with gemcitabine alone, although the combination regimen was superior with respect to response rate, progression-free survival, and clinical benefit.[209] Furthermore, the addition of oxaliplatin to FDR gemcitabine in the ECOG 6201 study did significantly improve survival compared with FDR gemcitabine alone.[201] Nevertheless, selected patients may benefit from this regimen because those with breast and ovarian cancers who have a *BRCA* mutation,[216,217] and some with inherited forms of pancreatic cancer,[218] may have disease that is particularly sensitive to a platinum agent. A retrospective study from Johns Hopkins of patients with metastatic pancreatic cancer and a family history of breast, ovarian, or pancreatic cancer suggested that response to gemcitabine and cisplatin was superior, even in those with one affected relative.[219]

Several randomized trials have investigated the combination of gemcitabine with a fluoropyrimidine in patients with advanced pancreatic cancer. The ECOG E2297 trial compared gemcitabine monotherapy with gemcitabine and bolus 5-FU/leucovorin in patients with advanced pancreatic cancer; no statistically significant survival advantage was observed for the combination regimen.[211] A randomized study in 533 patients with advanced cancer found that progression-free survival and objective response rates were significantly improved in patients receiving gemcitabine plus capecitabine compared with those receiving gemcitabine alone, although a trend toward an improvement in overall survival for the combination arm did not reach statistical significance.[215] Similarly, results from another smaller phase III trial evaluating this combination did not show an overall survival advantage for overall study population receiving combination gemcitabine and capecitabine, although a post-hoc analysis showed overall survival to be significantly increased in the subgroup of patients with good performance status.[206,220] Although concerns exist about dosing and toxicity of capecitabine in a United States population, results from a recent phase I/II study suggest that a biweekly regimen of fixed-dose gemcitabine in combination with capecitabine is both effective and well tolerated in patients with advanced disease.[221] Notably, results from several studies have indicated that the benefit of gemcitabine combination chemotherapy is predominantly seen in patients with good performance status.[206,208,213]

The panel considers gemcitabine-based combination therapy with a fluoropyrimidine to be a reasonable option for patients with locally advanced or metastatic disease and a good performance status who are interested in pursuing more aggressive therapy outside a clinical trial (see page 983). Furthermore, gemcitabine plus a platinum agent (i.e., cisplatin or oxaliplatin) may be a good choice in selected patients with disease characterized by hereditary risk factors (e.g., *BRCA* or *PALB2* mutations). However, the panel does not consider the combination of gemcitabine plus docetaxel[222] or gemcitabine plus irinotecan[210,222,223] to meet criteria for inclusion in the guidelines.

Although phase II trial results of gemcitabine combined with new targeted drugs (e.g., bevacizumab, cetuximab) were encouraging,[224,225] results of phase III studies of combinations of gemcitabine with a biologic agent have indicated that only the combination of gemcitabine plus erlotinib is associated with a statistically significant increase in survival compared with gemcitabine alone.[226–228] Results of the CALGB phase III trial evaluating gemcitabine and bevacizumab (an anti–vascular endothelial growth factor antibody) compared with gemcitabine plus placebo in patients with locally advanced or metastatic pancreatic cancer, and the SWOG phase III

randomized trial assessing cetuximab (which targets the epidermal growth factor receptor [EGFR]) plus gemcitabine versus gemcitabine alone did not show improvements in survival on addition of the biologic agent.[227] However, in a phase III trial of patients (n = 569) with advanced or metastatic pancreatic cancer randomly assigned to receive either erlotinib (an inhibitor of EGFR tyrosine kinase) plus gemcitabine or gemcitabine alone, patients in the combination arm showed statistically significant improvements in overall (HR, 0.82; $P = .038$) and progression-free survival (HR, 0.77; $P = .004$) compared with those receiving gemcitabine alone.[228] Median survival was 6.24 months and 1-year survival was 23%, compared with 5.91 months and 17% in the control arm. Adverse events, such as rash and diarrhea, were increased in the group receiving erlotinib.

A recent phase III trial comparing gemcitabine and erlotinib with or without bevacizumab in patients with metastatic pancreatic cancer did not show improved overall survival in either group, although a significant improvement in progression-free survival was observed with the addition of bevacizumab.[229] The FDA approved erlotinib in combination with gemcitabine for first-line treatment of patients with locally advanced unresectable or metastatic pancreatic cancer. The panel recommends gemcitabine/erlotinib combination therapy as an option for patients with locally advanced or metastatic disease and good performance status (category 2A; see pages 981, 982, and 983).

Results from the recently presented preplanned interim analysis of the phase III Prodige 4 ACCORD 11 trial evaluating the regimen of 5-FU, leucovorin, oxaliplatin, irinotecan (FOLFIRINOX) versus gemcitabine alone in patients with metastatic pancreatic cancer and good performance status showed dramatic improvements in both median progression-free (6.4 vs. 3.3 months; $P < .0001$) and median overall survival (11.1 vs. 6.8 months; $P < .0001$) in favor of the group receiving FOLFIRINOX.[230] However, some concerns exist about the toxicity of the FOLFIRINOX regimen (i.e., approximately one fourth of the patients receiving this regimen experienced grade 3/4 fatigue, 46% experienced grade 3/4 neutropenia, and 5.4% experienced grade 3/4 febrile neutropenia). Furthermore, whether these results can be generalized to the overall population of patients with metastatic pancreatic cancer and good performance status is unclear, because the percentage of patients with tumors of the pancreatic head enrolled in the trial was lower than typically observed in this population, raising the question of whether fewer patients had biliary stents. Nevertheless, further investigation of this very promising regimen is encouraged, particularly in the adjuvant setting.

Emerging data suggest that gemcitabine plus nab-paclitaxel,[231] and GTX[203] are effective and safe for use in the first-line treatment of patients with advanced pancreatic cancer.

Second-Line Therapy

As cross-sectional body imaging has improved, small volume metastatic disease is being detected in patients with pancreatic cancer who are otherwise maintaining good functional status. These patients may initially benefit from either gemcitabine-based or investigational therapy. However, these patients, and those with unresectable disease without detectable metastases, will ultimately progress, although a subset will continue to have sufficiently good performance status for second-line therapy to be considered.

Gemcitabine may offer palliative benefits in the second-line setting if patients have not been previously treated with gemcitabine.[232] For patients who have received prior gemcitabine-based therapy, the panel encourages treatment in a clinical trial. However, when investigational therapy is not available, treatment options for fluorinated pyrimidine–naïve patients include either capecitabine or 5-FU/leucovorin with or without oxaliplatin (see pages 981, 982, 983, and 988).[233–236] The capecitabine dose (1000 mg/m^2 by mouth twice daily) recommended in the algorithms (see page 989) is less than that described by Cartwright et al.,[235] because the higher dose has been associated with increased toxicity (e.g., diarrhea, hand–foot syndrome). Recent results from the phase III CONKO 003 trial showed significant improvements in both median progression-free (13 vs. 9 weeks; $P = .012$) and median overall survival (20 vs. 13 weeks; $P = .014$) when oxaliplatin was added to 5-FU/leucovorin,[233] making this regimen the standard approach for second-line therapy for patients without prior exposure to fluoropyrimidine-based therapy.

Recurrent Disease

For patients experiencing a recurrence following resection (see page 984), the panel recommends con-

sideration of confirmatory biopsy (category 2B). Chemoradiation can be considered if not previously administered in those patients with local disease recurrence only. In patients who have evidence of metastatic disease (with or without a local recurrence), treatment decisions are influenced by the length of time from completion of adjuvant therapy to the detection of metastases. If adjuvant therapy was completed fewer than 6 months before development of metastatic disease, the panel recommends that an alternative chemotherapy option be administered, although systemic therapy as previously administered is recommended when this period is greater than 6 months. In all cases of recurrent disease, a clinical trial is the preferred option and best supportive care should also be administered (see page 987).

Future Clinical Trials: Recommendations for Design

In 2007, a meeting was convened by the NCI's Gastrointestinal Cancer Steering Committee in recognition of the failure of several recent phase III trials to show clinically significant benefit for patients with pancreatic cancer, and to address the importance of integrating basic and clinical knowledge in the design of clinical trials for pancreatic cancer. Meeting participants included representatives from industry, government, and the community, and academic researchers and patient advocates. Several important themes that emerged from this meeting are summarized below, and the recommendations of the committee are endorsed by the panel.[237]

- With the emergence of new agents to treat pancreatic cancer, particularly biologics, clinical trial strategies incorporating principles of molecular biology and new imaging methods and results from preclinical studies are important.
- For patients enrolled in clinical trials, banking of tumor tissue samples should be required along with paired blood and serum samples.
- Biomarkers that serve as surrogate markers of the anticancer effects of investigational agents should be sought, and assays to measure these biomarkers should be well validated.
- Clinical trials should enroll homogeneous patient populations with respect to disease stage (i.e., separate trials for patients with locally advanced disease and metastatic disease) and patient performance status. Criteria for selecting study populations should take into account the putative differential efficacy of the agent (i.e., vaccines in patients with early-stage disease).
- Phase III trials should not be initiated in the absence of clinically meaningful efficacy and safety signals in the phase II setting.
- Phase II and III clinical trials should have a primary end point of overall survival.
- Quality control standards for preoperative imaging interpretation, pathologic assessment of tumor specimens, and surgical selection criteria are critical when evaluating adjuvant therapies.

Palliation of Locally Advanced and Metastatic Disease

A significant subset of patients with pancreatic cancer will require substantial palliative interventions that, in many respects, are unique to the disease. For patients with locally advanced unresectable and metastatic disease, the multidisciplinary management of symptoms caused by biliary obstruction, gastric outlet obstruction, and cancer-related pain is of primary importance (see page 987).

Biliary Obstruction

Approximately 65% to 75% of patients with pancreatic cancer develop symptomatic biliary obstruction.[238] For patients diagnosed with unresectable disease and biliary obstruction on initial evaluation, the best palliation is provided by an endoscopic biliary stent, especially when anticipated survival is limited. In most cases, a permanent stent is recommended unless biliary bypass is performed (see pages 979 and 981). Stent occlusion that causes recurrent cholangitis is a well-know complication of plastic biliary stents and typically occurs within 3 months of insertion. Metal stents are wider in diameter than temporary stents (i.e., have less likelihood of blockage) and become embedded in the bile duct, whereas plastic stents are more likely to become occluded but can be replaced. Results of a recent randomized controlled trial of 100 patients at a single center assigned to receive either a plastic stent or an uncovered self-expanding metal stent inserted endoscopically indicated that median patency times were 1.8 and 3.6 months (P = .002), respectively.[239] This conclusion is supported by results of a meta-analysis comparing metal and plastic

biliary stents placed endoscopically in patients with pancreatic adenocarcinoma characterized by biliary obstruction, which suggested that the risk of recurrent biliary obstruction was lower for the metal stents (relative risk, 0.52; 95% CI, 0.39–0.69), although no significant differences in technical/therapeutic success, complications, or 30-day mortality rates were found.[240]

When a biliary stent cannot be placed (often because the endoscope cannot be advanced past the neoplasm that is obstructing the gastric outlet), percutaneous biliary drainage with subsequent internalization may be necessary. An alternative is to sequentially dilate the duodenum endoscopically, place a metallic biliary stent, and then place an enteral stent.[241] Durable palliation of biliary obstruction can often be achieved with an expandable metallic biliary endoprosthesis (e.g., Wallstent; Boston Scientific, Natick, Massachusetts).[241]

For patients with jaundice and potentially resectable disease who are found to have unresectable tumors after laparotomy, an open biliary-enteric bypass provides durable palliation of biliary obstruction and can be combined with procedures that palliate symptoms resulting from gastric outlet obstruction and cancer-related pain (see pages 979 and 987). The panel recommends an open biliary-enteric bypass with or without duodenal bypass (category 2B for prophylactic duodenal bypass) and with or without open ethanol celiac plexus block (category 2B). Bypass of the common bile duct (choledochojejunostomy) or common hepatic duct (hepaticojejunostomy) to the jejunum is preferred to bypass of the gallbladder (cholecystojejunostomy) because choledochojejunostomy/hepaticojejunostomy provides more durable and reliable palliation of biliary obstruction.[238]

Gastric Outlet Obstruction

Symptomatic gastric outlet obstruction occurs in 10% to 25% of patients with pancreatic cancer.[238] Patients found to have locally advanced or metastatic disease on evaluation who develop gastric outlet obstruction may be palliated with an endoscopically placed enteral stent, especially if their life expectancy is limited or their performance status is poor.[241] An alternative for these patients is percutaneous endoscopic gastrostomy tube placement. For a fit patient with a life expectancy greater than 3 to 6 months (i.e., locally advanced disease), a laparoscopic gastrojejunostomy with or without a jejunostomy tube should be considered, because it may provide more durable and effective palliation of gastric outlet obstruction than an enteral stent. Nevertheless, placement of an enteral stent is also an option for these patients (see page 987).

In patients with potentially resectable disease who undergo a laparotomy and are found to have unresectable disease, a palliative gastrojejunostomy should be performed for those deemed to be at risk of developing symptomatic gastric outlet obstruction. The role of prophylactic gastrojejunostomy has been evaluated in otherwise asymptomatic patients who are found to be unresectable at laparotomy. Two randomized controlled trials have investigated the role of prophylactic gastrojejunostomy for unresectable periampullary cancer, with most arising from the head of the pancreas.[242,243] In both studies, approximately 20% of patients who did not undergo a prophylactic gastrojejunostomy developed late gastric outlet obstruction that required therapy. In both studies, prophylactic retrocolic gastrojejunostomy significantly decreased the incidence of late gastric outlet obstruction but did not extend the length of stay or increase complication rates, such as delayed gastric emptying.

If staging laparoscopy shows unresectable disease, palliation of symptoms may be provided by a laparoscopic gastrojejunostomy, with or without laparoscopic biliary bypass, depending on life expectancy and surgical expertise.

Severe Tumor-Associated Abdominal Pain

Most patients with locally advanced or metastatic pancreatic cancer experience cancer-related pain.[244] General principles for cancer-related pain management can be found in the NCCN Clinical Practice Guidelines (NCCN Guidelines) on Adult Cancer Pain (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). Because advanced pancreatic cancer often infiltrates the retroperitoneal nerves of the upper abdomen, celiac plexus neurolysis should be considered.

In 2 randomized controlled trials, celiac plexus neurolysis significantly improved pain relief in patients with advanced pancreatic cancer.[244,245] Minimally invasive techniques include EUS-guided and percutaneous fluoroscopic- or CT-guided celiac plexus neurolysis (see page 987), but laparoscopic, thoracoscopic, and open approaches can also be used.

If staging laparoscopy reveals unresectable disease, palliation of tumor-associated abdominal pain may be provided by laparoscopic celiac plexus neurolysis, depending on life expectancy and surgical expertise. In selected patients with severe local back pain, radiation therapy may be considered, even in the setting of metastatic disease.

Additional Palliative Interventions

Pancreatic Insufficiency: Exocrine enzyme insufficiency in pancreatic cancer is caused by tumor-induced damage to the pancreatic parenchyma and/or pancreatic duct, and surgical removal of pancreatic tissue.[246,247] Oral pancreatic exocrine enzyme replacement therapy is recommended for patients with pancreatic cancer who have symptoms of exocrine enzyme deficiency (e.g., steatorrhea; see page 987).

Treatment of Thromboembolic Disease: The risk of developing venous thromboembolic disease is substantially increased in patients with pancreatic cancer.[248] The panel recommends low-molecular-weight heparin (LMWH) as preferred therapy over Coumadin for patients with pancreatic cancer who develop a venous thromboembolism (VTE; see page 987). Support for this recommendation comes from results of 2 large prospective randomized clinical trials: CLOT and CONKO 004. In the CLOT study, an approximately twofold decrease in the incidence of recurrent VTE at 6 months was observed in patients with advanced or metastatic cancer diagnosed with a VTE who were treated with the LMWH dalteparin, compared with those treated with an oral anticoagulant.[249] In the CONKO 004 trial, VTE- and chemotherapy-naïve patients with advanced pancreatic cancer were randomized to receive palliative chemotherapy either with or without enoxaparin.[250] The risk of developing symptomatic VTE was significantly lower for patients in the LMWH arm of the study, with no significant increase in bleeding observed in this group compared with those not receiving enoxaparin.

Depression, Pain, Malnutrition: The panel recommends that patients with locally advanced or metastatic pancreatic cancer undergo a formal evaluation by a palliative medicine service when appropriate (see page 987). Additional resources are detailed in the NCCN Guidelines on Palliative Care, Adult Cancer Pain, and Distress Management (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Surveillance

Although data on the role of surveillance in patients with resected pancreatic adenocarcinoma are limited, recommendations were based on the consensus that earlier identification of disease may facilitate patient eligibility for investigational studies or other forms of treatment. The panel recommends a history and physical examination be performed for symptom assessment every 3 to 6 months for 2 years (see page 980). Although the panel discussed the role of CA 19-9 determinations and follow-up CT scans every 3 to 6 months for 2 years after surgical resection, consensus was not uniform on whether this was appropriate (i.e., these recommendations are category 2B), because data are not available to show that earlier treatment of recurrences, after detection through increased tumor marker levels or CT scan, leads to better patient outcomes.

Summary

Overall, in view of the relatively high likelihood of a poor outcome for patients with all stages of pancreatic cancer, the panel recommends that investigational options be considered in all phases of disease management. Specific palliative measures are recommended for patients with advanced pancreatic adenocarcinoma characterized by biliary or gastric obstruction, severe abdominal pain, or other tumor-associated manifestations of the disease.

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Individual Disclosures of the NCCN Pancreatic Adenocarcinoma Panel					
Panel Member	**Clinical Research Support**	**Advisory Boards, Speakers Bureau, Expert Witness, or Consultant**	**Patent, Equity, or Royalty**	**Other**	**Date Completed**
J. Pablo Arnoletti, MD	OSI Pharmaceuticals, Inc.	None	None	None	12/2/09
Stephen Behrman, MD	None	None	None	None	12/16/09
Edgar Ben-Josef, MD	None	None	None	None	9/30/09
Al B. Benson III, MD	Abbott Laboratories; Amgen Inc.; AstraZeneca Pharmaceuticals LP; Bayer HealthCare; Bristol-Myers Squibb Company; Eli Lilly and Company; Enzon Pharmaceuticals; Genentech, Inc.; General Electric; Genomic Health, Inc.; ImClone Systems Incorporated; National Cancer Institute; Novartis Pharmaceuticals Corporation; Onyx Pharmaceuticals, Inc.; Pfizer Inc.; Roche Laboratories, Inc.; sanofi-aventis U.S.; and Taiho Parmaceuticals Co., Ltd.	Abbott Laboratories; Amgen Inc.; AstraZeneca Pharmaceuticals LP; Bayer HealthCare; Bristol-Myers Squibb Company; Eli Lilly and Company; Enzon Pharmaceuticals; Genentech, Inc.; General Electric; Genomic Health, Inc.; ImClone Systems Incorporated; National Cancer Institute; Novartis Pharmaceuticals Corporation; Onyx Pharmaceuticals, Inc.; Pfizer Inc.;Roche Laboratories, Inc.; sanofi-aventis U.S.; and Taiho Parmaceuticals Co., Ltd.	None	None	12/3/09
Jordan D. Berlin, MD	Abbott Laboratories; Bayer HealthCare; Genentech, Inc.; ImClone Systems Incorporated; Merck & Co., Inc.; and Pfizer	Amgen Inc.; AstraZeneca Pharmaceuticals LP; Merck & Co., Inc.; Agensys/Seattle Genetics; Clovis; Roche Laboratories, Inc.; and Schering-Plough Corporation	None	None	4/9/10
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