National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Pancreatic Adenocarcinoma

V.1.2008

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References

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

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

SUMMARY OF GUIDELINES UPDATES

Summary of changes in the 2008 version of the Pancreatic Adenocarcinoma guidelines from the 1.2007 version include:

PANC-2

- Removed the category 2B level of consensus from preoperative CA 19-9 recommendation in the work-up section.
- Modified footnote "a" to read: CA 19-9 may be falsely positive in cases of benign biliary obstruction or falsely undetectable in Lewis-a negative individuals.

PANC-3

- Changed the formatting of the pathway for Borderline resectable, (no jaundice) to include separate decision pathways for planned neoadjuvant therapy (category 2B) and planned resection (category 2B).
- Added footnote "d": Consider neoadjuvant therapy on clinical trial.
- Added footnote "e": The majority of NCCN institutions prefer upfront neoadjuvant therapy in the setting of borderline resectable disease.

PANC-4

- Changed adjuvant treatment recommendations to: Chemoradiation (5-FU-based) + systemic gemcitabine or Chemotherapy alone: Gemcitabine preferred or 5-FU or Capecitabine (all category 2A).
- Reworded footnote "i": Adjuvant treatment should be administered to patients who have not had neoadjuvant therapy and who have adequately recovered from surgery; treatment should be initiated within 4-8 weeks. If systemic chemotherapy precedes chemoradiation, consider restaging with a CT scan prior to radiation. Patients who have received neoadjuvant chemoradiation are candidates for adjuvant chemotherapy alone following surgery.

PANC-5

- Modified footnote "p": For fluorinated pyrimidine naive patients. Gemcitabine is also an option for patients who received 5-FU chemoradiation and no additional chemotherapy.

PANC-5

- Added separate decision pathway for salvage therapy based on patient performance status.

PANC-6

- Changed the formatting of the pathway for Borderline resectable, (jaundice) to include separate decision pathways for planned neoadjuvant therapy (category 2B) and planned resection (category 2B).
- Added footnote "d": Consider neoadjuvant therapy on clinical trial.
- Added footnote "e": The majority of NCCN institutions prefer upfront neoadjuvant therapy in the setting of borderline resectable disease.

PANC-A

- Added principle #3 on use of EUS for staging of disease and on use of defined pancreas protocol when CT is used for staging.
- Modified #4: 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.

PANC-B

- Clarified statement relating to nodal status as a criterion in defining resectability status with statement.

PANC-D

- Added CapeOx as a second-line therapy option
- Specified that gemcitabine combination therapy is recommended for patients with good performance status only.

PANC-E

- New to the guidelines, Principles of Palliation and Supportive Care

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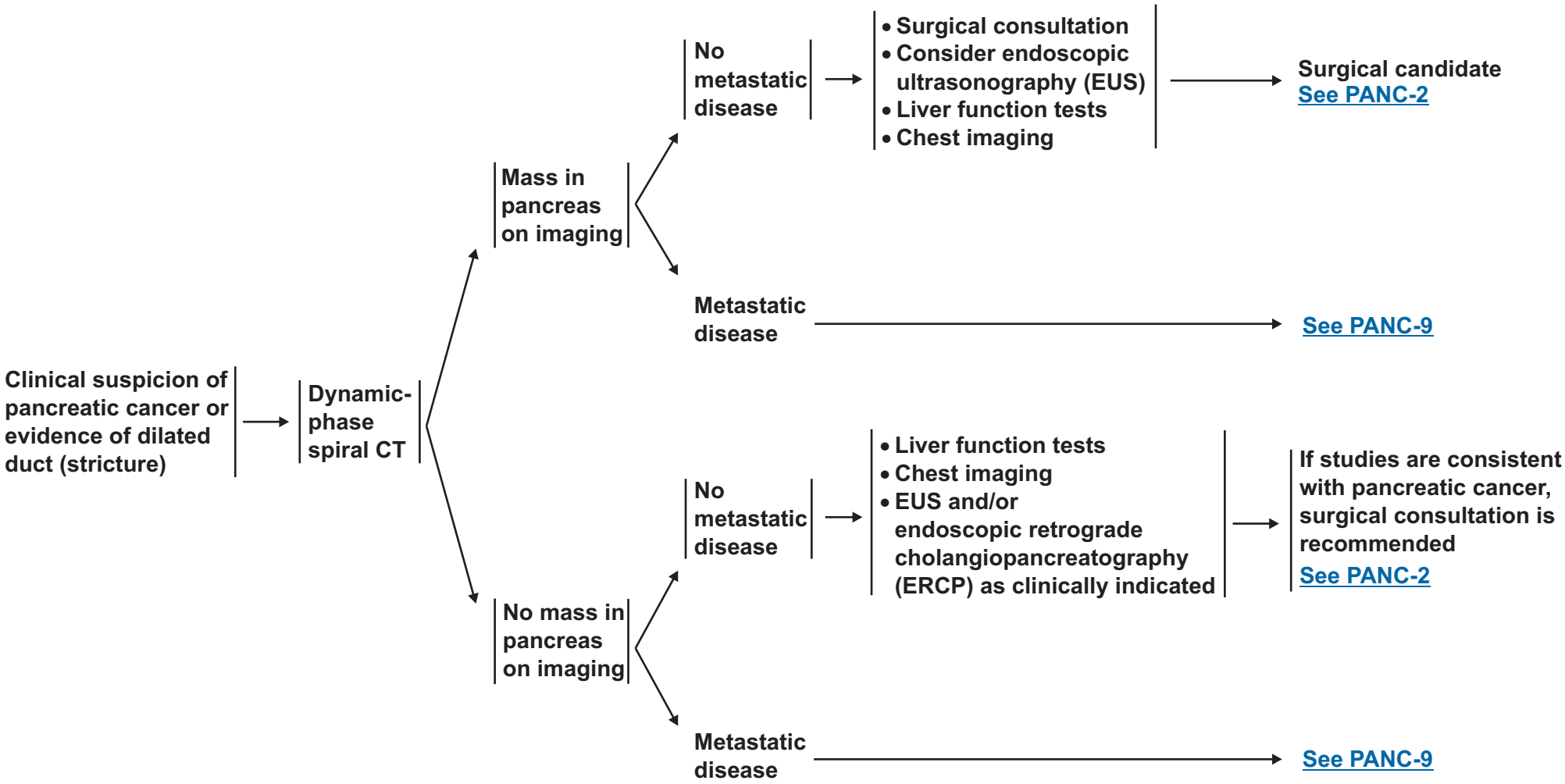
Pancreatic Adenocarcinoma

CLINICAL PRESENTATION

WORKUP



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Pancreatic Adenocarcinoma

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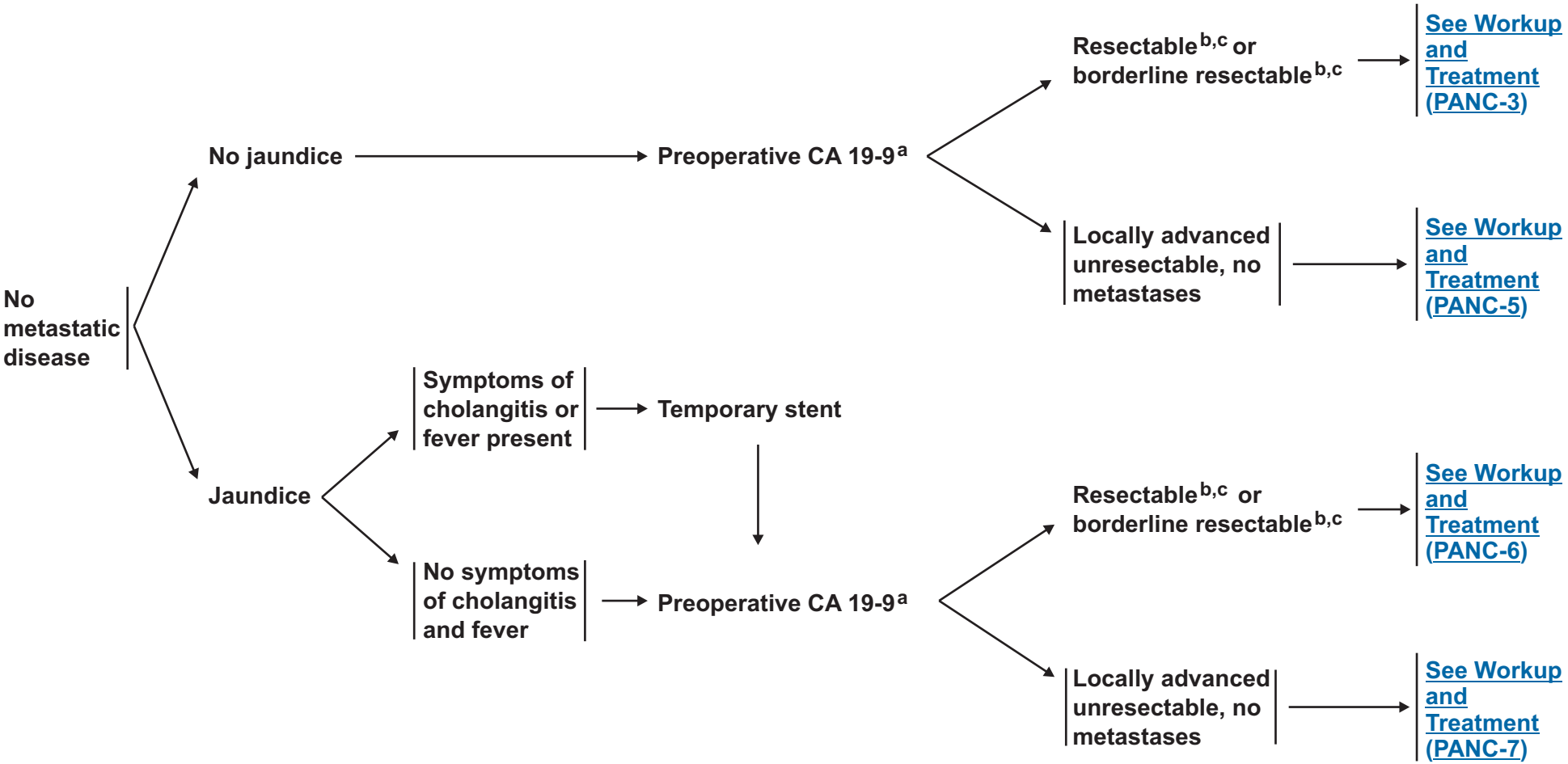
WORKUP



[a] CA 19-9 may be falsely positive in cases of benign biliary obstruction or falsely undetectable in Lewis-a negative individuals.
[b] See Principles of Diagnosis and Staging (PANC-A).
[c] See Criteria Defining Resectability Status (PANC-B).

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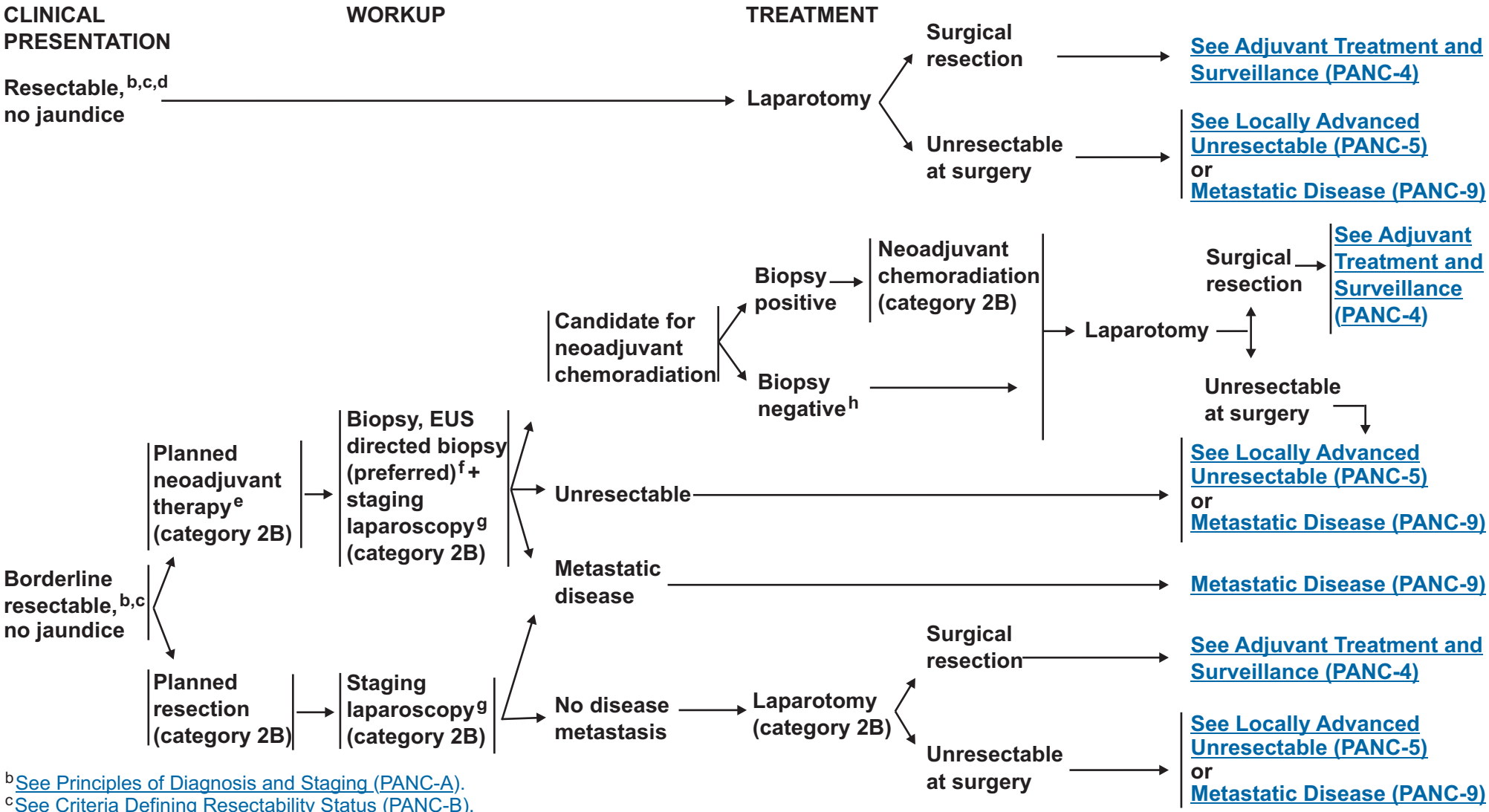
Pancreatic Adenocarcinoma



[b] See Principles of Diagnosis and Staging (PANC-A).
[c] See Criteria Defining Resectability Status (PANC-B).
[d] Consider neoadjuvant therapy on clinical trial.
[e] The majority of NCCN institutions prefer upfront neoadjuvant therapy in the setting of borderline resectable disease.
[f] See Principles of Diagnosis and Staging #1 and #4 (PANC-A).
[g] See Principles of Diagnosis and Staging #5 (PANC-A).
[h] A negative biopsy should be confirmed by at least one repeat EUS biopsy.

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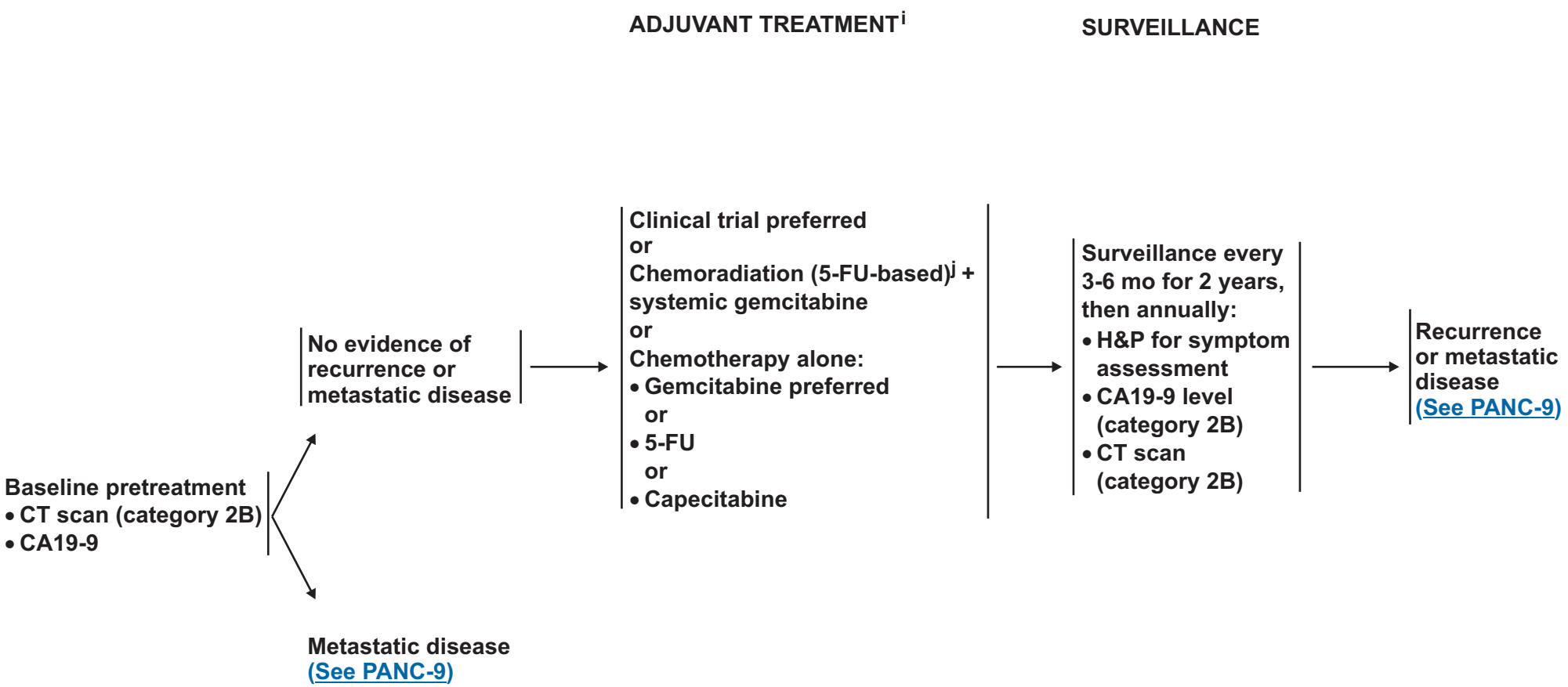
Pancreatic Adenocarcinoma



[i] Adjuvant treatment should be administered to patients who have not had neoadjuvant therapy and who have adequately recovered from surgery; treatment should be initiated within 4-8 weeks. If systemic chemotherapy precedes chemoradiation, consider restaging with a CT scan prior to radiation. Patients who have received neoadjuvant chemoradiation are candidates for adjuvant chemotherapy alone following surgery.

[j] See Principles of Radiation Therapy (PANC-C).

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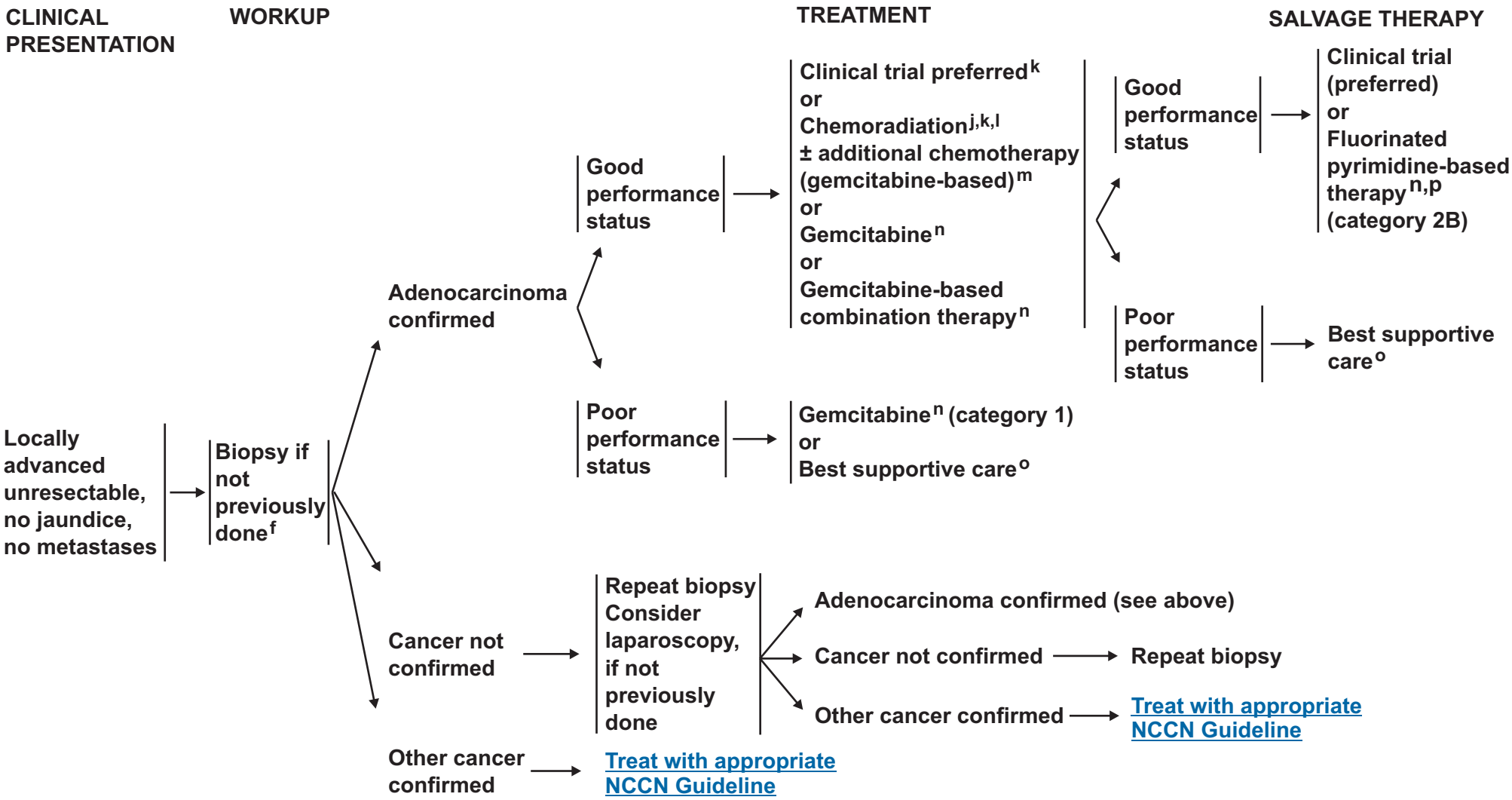

[f] See Principles of Diagnosis and Staging #1 and #4 (PANC-A).
[j] See Principles of Radiation Therapy (PANC-C).
[k] Laparoscopy as indicated to evaluate distant disease.
[l] Patients with a significant response to chemoradiation may be considered for surgical resection, although there is no definitive evidence at this time to support this intervention
[m] Randomized clinical trial data at this time are inconclusive.
[n] See Principles of Chemotherapy (PANC-D).
[o] See Principles of Palliation and Supportive Care (PANC-E).
[p] For fluorinated pyrimidine naive patients. Gemcitabine is also an option for patients who received 5-FU chemoradiation and no additional chemotherapy.

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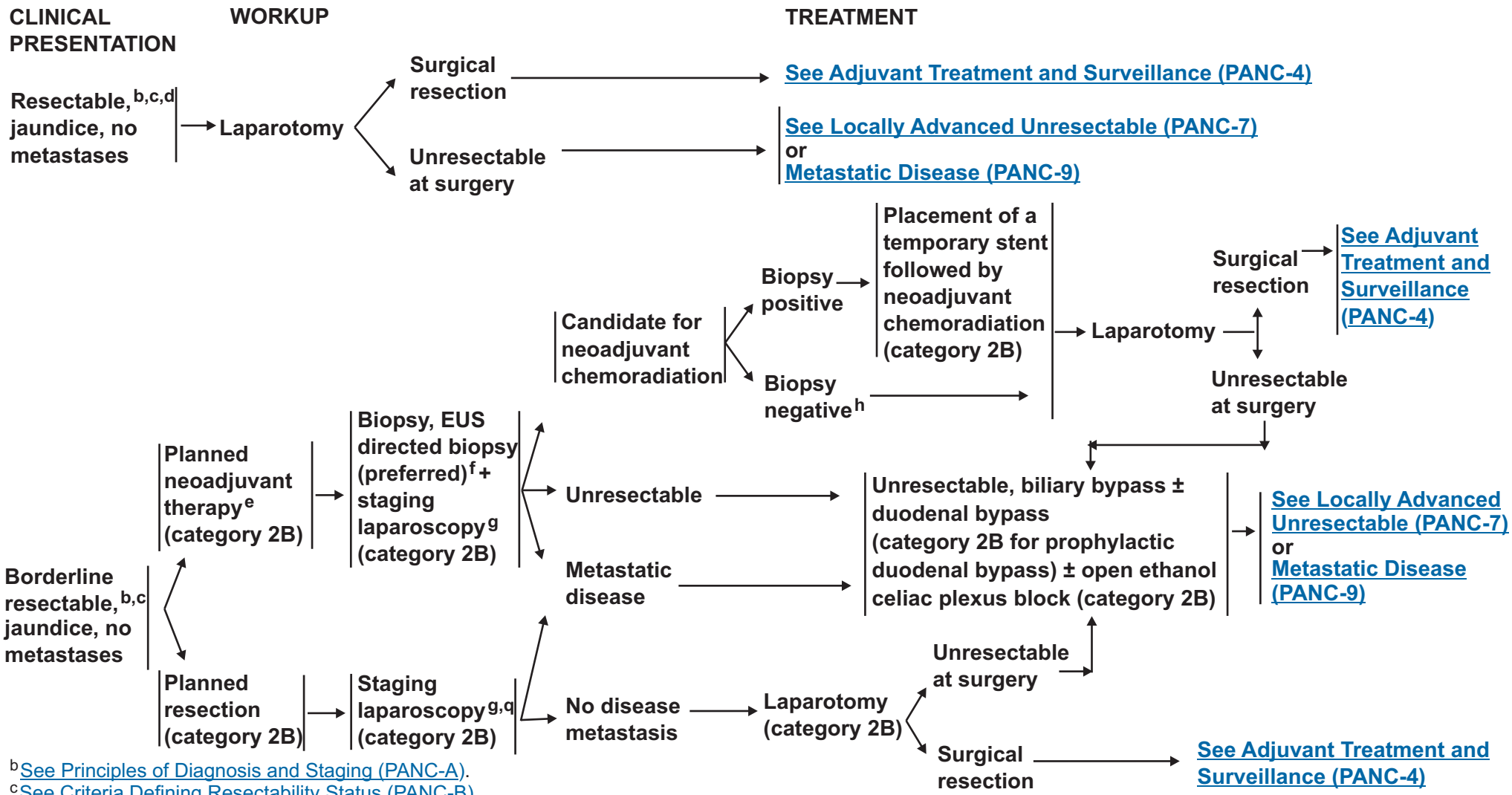

[b] See Principles of Diagnosis and Staging (PANC-A).
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[e] The majority of NCCN institutions prefer upfront neoadjuvant therapy inthe setting of borderline resectable disease.
[f] See Principles of Diagnosis and Staging #1 and #4 (PANC-A).
[g] See Principles of Diagnosis and Staging #5 (PANC-A).
[h] A negative biopsy should be confirmed by at least one repeat EUS biopsy.
[q] Biliary bypass may be performed at the time of laparoscopy.

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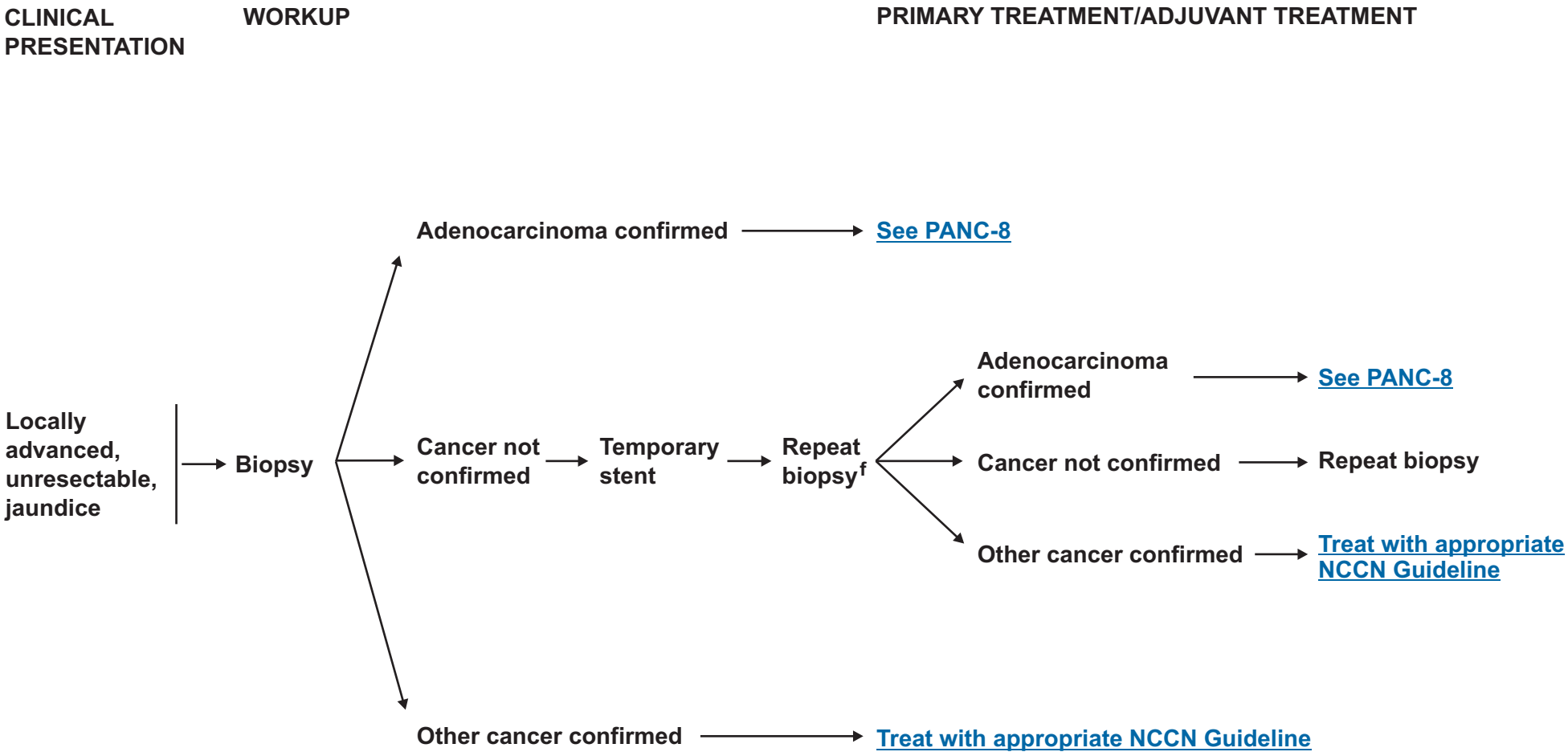

[f] See Principles of Diagnosis and Staging #1 and #4 (PANC-A).

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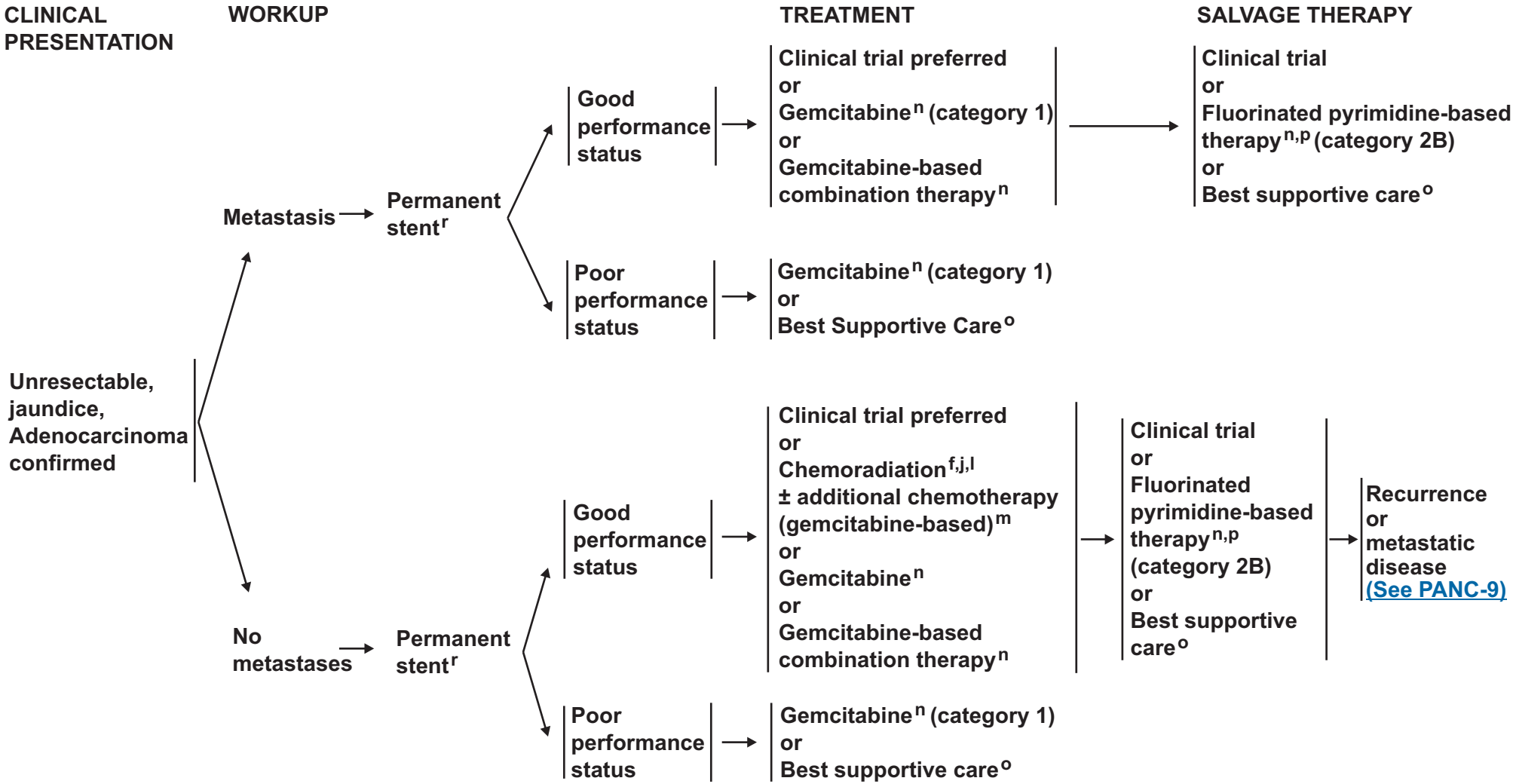

[f] See Principles of Diagnosis and Staging #1 and #4 (PANC-A).
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[l] Patients with a significant response to chemoradiation may be considered for surgical resection, although there is no definitive evidence at this time to support this intervention.
[m] Randomized clinical trial data at this time are inconclusive.
[n] See Principles of Chemotherapy (PANC-D).
[o] See Principles of Palliation and Supportive Care (PANC-E).
[p] For fluorinated pyrimidine naive patients. Gemcitabine is also an option for patients who received 5-FU chemoradiation and no additional chemotherapy.
[r] Unless biliary bypass performed at time of laparoscopy or laparotomy.

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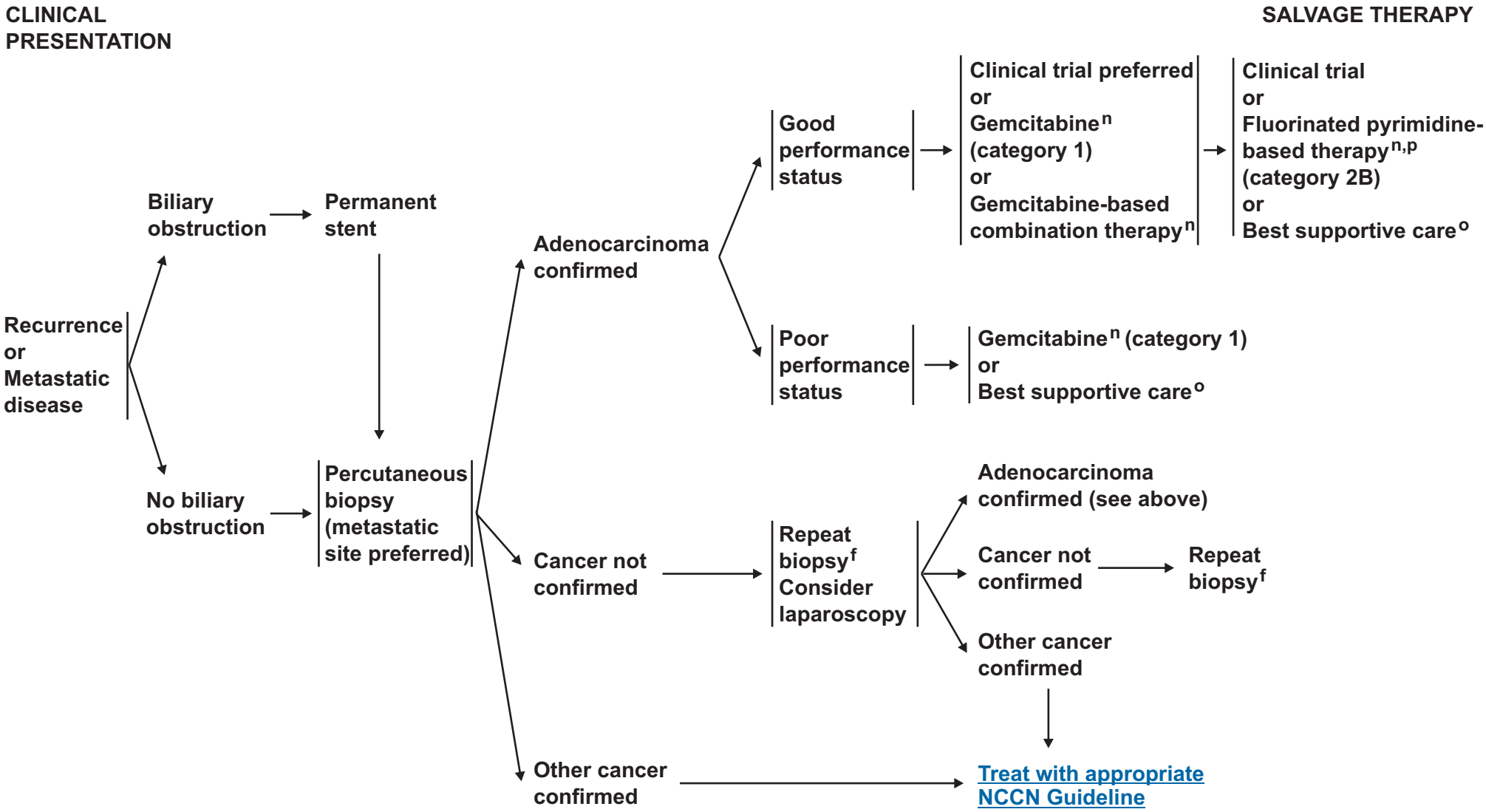
Pancreatic Adenocarcinoma



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[p] For fluorinated pyrimidine naive patients.

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Pancreatic Adenocarcinoma

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.

#2 Resections should be done at institutions that perform a large number (>20) of pancreatic resections annually.

#3 Endoscopic ultrasound (EUS) may be complementary to CT for staging. CT should be performed according to a defined pancreas protocol such as triphasic cross-sectional imaging and thin slices).

#4 EUS-directed FNA biopsy is preferable to a CT-guided FNA in patients with resectable disease because of the much lower risk of peritoneal seeding with EUS FNA when compared 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.

#5 Diagnostic staging laparoscopy to rule out subradiologic metastases (especially for body and tail lesions) is used routinely in some institutions prior to surgery or chemoradiation, or selectively in patients who are at higher risk for disseminated disease (borderline resectable disease, markedly elevated CA19-9 or large primary tumors).

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

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Pancreatic Adenocarcinoma

CRITERIA DEFINING RESECTABILITY STATUS

RESECTABLE

- HEAD/BODY/TAIL
  - No distant metastases
  - Clear fat plane around celiac and superior mesenteric arteries (SMA)
  - Patent superior mesenteric vein (SMV)/portal vein

BORDERLINE RESECTABLE[1]

- HEAD/BODY
  - Severe unilateral SMV/portal impingement
  - Tumor abutment on SMA
  - Gastroduodenal artery (GDA) encasement up to origin at hepatic artery
  - Tumors with limited involvement of the IVC
  - SMV occlusion, if of a short segment, with open vein both proximally and distally (If the proximal SMV were occluded up to the portal vein branches then it would be unresectable)
  - Colon or mesocolon invasion
- TAIL
  - Adrenal, colon or mesocolon, or kidney invasion (category 2B)

UNRESECTABLE

- HEAD
  - Distant metastases
  - SMA, celiac encasement
  - SMV/portal occlusion
  - Aortic, Inferior vena cava (IVC) invasion or encasement
  - Invasion of SMV below transverse mesocolon
- BODY
  - Distant metastases
  - SMA, celiac, hepatic encasement
  - SMV/portal occlusion
  - Aortic invasion
- TAIL
  - Distant metastases
  - SMA, celiac encasement
  - Rib, vertebral invasion
- Nodal status
  - Metastases to lymph nodes beyond the field of resection should be considered unresectable.

[1] For any tumors where there is a higher likelihood of an incomplete (R1 or R2) resection, it is suggested that chemoradiation be given prior to surgery.

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PRINCIPLES OF RADIATION THERAPY

ADJUVANT RT

In contrast to the GITSG trial,[1] 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.[2] However, these trials have been criticized widely for lack of statistical power (EORTC)[3] and serious flaws in conduct and reporting (ESPAC). Therefore, 5-FU based chemoradiotherapy as part of adjuvant therapy remains an acceptable choice.

- **Use of CT simulation and 3D 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/day)**

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 3D treatment planning is strongly encouraged**
- **Treatment volumes should be based on CT scans and surgical clips (when placed)**
- **When 5-FU based radiochemotherapy is employed, 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/day)**

[1] GITSG 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.

[2] ESPAC-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.

[3] EORTC 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.

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PRINCIPLES OF CHEMOTHERAPY

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

- **Goals of systemic therapy should be discussed with patients prior to initiation of therapy and enrollment in a clinical trial is strongly encouraged.**
- **Close follow-up of patients undergoing chemotherapy is indicated.**
- **Gemcitabine at 1000 mg/m^2 over 30 minutes, weekly for 3 weeks every 28 days, is considered standard front-line therapy for patients with metastatic disease (category 1).**
- **Gemcitabine or gemcitabine-based combination therapy without RT may be considered as an alternative to 5-FU-based chemoradiation for patients with locally advanced, unresectable disease or as adjuvant therapy.**
- **Fixed-dose rate gemcitabine (10 mg/m^2/minute) may substitute for standard infusion of gemcitabine over 30 minutes (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[2]**
  - **Gemcitabine + fluoropyrimidine[2,3]**
- **Second-line therapy may consist of gemcitabine for those patients not previously treated with the drug. Other options include capecitabine[4] (1000 mg/m^2 PO twice daily, days 1-14 every 21 days) or FOLFOX[5] or CapeOx[6] (all category 2B).**
- **The CONKO trial supports the use of post-operative gemcitabine as adjuvant chemotherapy in resectable pancreatic adenocarcinoma.[7] The use of gemcitabine based chemotherapy is frequently combined, sequentially, with 5-FU based chemoradiotherapy.**

[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, Hinke A, Bock S, et al. Benefit of gemcitabine-based combination treatment in advanced pancreatic cancer: a meta analysis of randomized trials. 2007 Gastrointestinal Cancers Symposium. Abstract 129.

[3] Cunningham D, Chau I, Stocken D, et al. Phase III randomised comparison of gemcitabine (GEM) versus gemcitabine plus capecitabine (GEM-CAP) in patients with advanced pancreatic cancer. European Cancer Conference (ECCO 13), presentation/abstract PS11, Paris, France, 2005 November 2. European Journal of Cancer Supplements 2005;3:4.

[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] Oettle H, Pelzer U, Stieler J, et al. Oxaliplatin/folinic acid/5-fluorouracil [24h] (OFF) plus best supportive care versus best supportive care alone (BSC) in second-line therapy of gemcitabine-refractory advanced pancreatic cancer (CONKO 003). J Clin Oncol (Meetings Abstracts) 2005;23:4031.

[6] Xiong HQ, Wolff RA, Hess KR, et al. A phase II trial of oxaliplatin plus capecitabine (xelox) as second-line therapy for patients with advanced pancreatic cancer. J Clin Oncol. 2006; 24: no. 185 (June 20 suppl). Abstract 4119.

[7] CONKO trial: Oettle, H, Post, S, Neuhaus, P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: A randomized controlled trial. JAMA 2007;297:267-277.

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PRINCIPLES OF PALLIATION AND SUPPORTIVE CARE

Objectives: 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
  - Poor performance status
    - Enteral stent
    - PEG tube

- Severe tumor-associated abdominal pain
  - EUS-guided celiac plexus neurolysis (fluoroscopic- or CT-guided if unavailable)

- Depression, pain, malnutrition
  - Formal Palliative Medicine Service evaluation when appropriate (See NCCN Supportive Care Guidelines)

- Pancreatic insufficiency
  - Pancreatic enzyme replacement

- Thrombembolic disease
  - Low molecular weight heparin preferred over warfarin

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Staging

Table 1

American Joint Committee on Cancer (AJCC)
TNM Staging of Pancreatic Cancer (2002)

Because only a few patients with pancreatic cancer undergo surgical resection of the pancreas (and adjacent lymph nodes), a single TNM classification must apply to both clinical and pathologic staging.

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma *in situ**
T1 Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2 Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3 Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

*This also includes the "PanInIII" classification.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Stage Grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

STAGING CONTINUED ON ST-2

Table 1 continued

Histopathologic Type

The staging system applies to all exocrine carcinomas that arise in the pancreas. It does not apply to endocrine tumors, which usually arise from the islets of Langerhans. Carcinoid tumors are also excluded. More than 90% of malignant tumors of the pancreas are exocrine carcinomas. The following carcinomas are included:

- Severe ductal dysplasia/carcinoma in situ (PanIn III; pancreatic intraepithelial neoplasia)
- Ductal adenocarcinoma
- Mucinous noncystic carcinoma
- Signet ring cell carcinoma
- Adenosquamous carcinoma
- Undifferentiated carcinoma (Spindle and giant cell types; Small cell types)
- Mixed ductal-endocrine carcinoma
- Osteoclast-like giant cell tumor
- Serous cystadenocarcinoma
- Mucinous cystadenocarcinoma
- Intraductal papillary mucinous carcinoma with or without invasion (IPMN)
- Acinar cell carcinoma
- Acinar cell cystadenocarcinoma
- Mixed acinar-endocrine carcinoma
- Pancreaticoblastoma
- Solid pseudopapillary carcinoma
- Borderline (uncertain malignant potential) tumors (Mucinous cystic tumor with moderate dysplasia; Intraductal papillary-mucinous tumor with moderate dysplasia; Solid pseudopapillary tumor)
- Other

Histologic Grade (G)

GX Grade cannot be assessed

G1 Well differentiated

G2 Moderately differentiated

G3 Poorly differentiated

G4 Undifferentiated

Manuscript

NCCN Categories of Evidence and Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

During the year 2007, an estimated 33,370 people will die of pancreatic cancer in the United States.[1] This disease is the fourth most common cause of cancer-related death among U.S. men.[1] Its peak incidence occurs in the seventh and eighth decades of life. Although incidence is roughly equal in the two sexes, African Americans appear to have a higher incidence of pancreatic cancer than white Americans.[2] In these NCCN Pancreatic Adenocarcinoma guidelines, only tumors of the exocrine pancreas are discussed; neuroendocrine tumors are not included.

By definition, the NCCN practice 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 members of the Panel during the process of developing these guidelines. A 5% rule (omitting clinical scenarios that comprise less than 5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from these guidelines.

Risk Factors and Genetic Predisposition

Although the increase in risk is small, pancreatic cancer is firmly linked to cigarette smoking.[3] There are no clear dietary risk factors; however, dietary fat has been implicated in experimental models,[4] and an increased body mass index is associated with increased risk.[5,6] Occupational exposure to chemicals, such as beta-naphthylamine and benzidine, is also associated with an increased risk of pancreatic cancer.[7]

The relationship among diabetes mellitus, alcohol intake, and chronic pancreatitis with adenocarcinoma of the pancreas has been a topic of great debate. Increasingly, it appears that hyperglycemia is probably a result of pancreatic cancer in most patients.[8,9] Chronic pancreatitis has long been thought to be a risk factor for pancreatic cancer[10]; however, results from the International Pancreatitis Study[11] suggest that the long-term risk of pancreatic cancer in patients with chronic pancreatitis may actually be related to alcohol consumption, smoking, and selection bias. True familial pancreatic cancer is rare; however, a genetic predisposition may be present in up to 5% of patients,[12] and familial excess of pancreatic cancer is associated with high risk. A mutation of the p16 germline has been reported in families with pancreatic cancer and melanoma.[12,13] An excess of pancreatic cancer is also seen in families harboring BRCA-2 (breast cancer susceptibility gene--2) mutations.[14] Asymptomatic individuals at high risk for pancreatic cancer (ie, have first-degree relatives with cancer) were assessed using endoscopic ultrasound (EUS) in the Cancer of the Pancreas Screening 2 (CAPS2) project. Premalignant or preinvasive pancreatic neoplasms were detected suggesting that EUS may have a promising role in screening high-risk patients.[15]

Diagnosis and Staging

Ductal adenocarcinoma and its variants account for over 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.[16,17] Thus, pancreatic carcinoma should be considered in diabetic patients with unusual manifestations, such as abdominal symptoms and continuous weight loss.[18] Pancreatic cancer is usually diagnosed after identification of a mass or evidence of a dilated duct (stricture) in the pancreas using transabdominal ultrasonography or computed tomography (CT). Pancreatitis and other benign conditions (eg, interpapillary mucinous neoplasm) are in the differential diagnosis.[19-21]

Preoperative Imaging Evaluations

Preoperative staging to assess the extent of disease is of paramount importance. All of the NCCN institutions represented on the Pancreatic Cancer Panel agreed that all patients for whom there is clinical suspicion of pancreatic cancer or evidence of a dilated duct (stricture) should undergo initial evaluation by dynamic-phase helical or spiral CT performed according to a defined pancreas protocol (ie, triphasic cross-sectional imaging and thin slices) (see PANC-1; PANC-A).[22,23] This high-resolution technology has been reported to predict a high resectability rate (80%), presuming that the following radiologic criteria are met: (1) no evidence of extrapancreatic disease; (2) evidence of nonobstructive superior mesenteric-portal vein confluence; and (3) no evidence of direct tumor extension to the celiac axis and superior mesenteric artery (SMA).[24] Other studies have shown that 70%-85% of patients determined by CT imaging to have resectable tumors were able to undergo resection.[25,26]

Patients with a mass in the pancreas on dynamic-phase spiral CT, but no evidence of metastatic disease, should also receive a surgical consultation. Technical improvements in ultrasonography have led to the development of EUS which may provide useful staging information in pancreatic cancer, particularly through assessment of certain types of vascular invasion.[27,28] 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 done with EUS (eg, celiac block, removal of ascites). It was the consensus of the Panel that whereas the accuracy of EUS in assessing involvement of certain veins (eg, portal vein) is high, this technique is less accurate in imaging tumor invasion of the superior mesenteric artery (SMA).[28,29]

Patients without a mass in the pancreas on imaging and without evidence of metastatic disease should undergo additional imaging with endoscopic retrograde cholangiopancreatography (ERCP) or EUS if clinically indicated. If studies are consistent with pancreatic cancer, then surgical consultation is recommended. ERCP is a useful diagnostic tool in patients for whom the CT scan is equivocal, because fewer than 3% of patients with pancreatic carcinoma have normal pancreatograms.[30] It can be difficult to discriminate between benign and malignant strictures or stenosis; however, severe stenosis and marked proximal dilatation more often indicate malignancy.[31] Stent placement at the time of ERCP can also be used to palliate biliary obstruction when surgery is not elected, or if surgery must be delayed. Magnetic resonance cholangiopancreatography has a role if ERCP is not technically feasible. Preoperative staging is usually done with a high-resolution spiral or helical CT scan. In cases where CT is not possible

or relatively contraindicated, magnetic resonance imaging with gadolinium infusion can be used.

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 high-resolution spiral CT scans.[32] The Panel considers positive cytology from washings obtained at laparoscopy or laparotomy to be equivalent to M1 disease.[33] The value of a staging laparoscopy in patients with resectable/borderline resectable disease was debated by the Panel, and it is included as a category 2B recommendation. For borderline resectable lesions or poor prognostic factors (eg, markedly elevated CA 19-9, large primary tumor, and tumors in the body and tail), additional staging with laparoscopy is less controversial.

NCCN institutions vary in the use of additional staging technologies, such as EUS and laparoscopy. The role of EUS in staging is felt 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.[22] Because these procedures are operator dependent, some divergence in use may occur because of differing technical capabilities and available expertise. Chest imaging is recommended as part of the preoperative workup of patients without evidence of abdominal metastases on CT to evaluate for the presence of pulmonary metastases.[34]

Tumor-Associated Antigens

Many tumor-associated antigens have been studied in connection with pancreatic adenocarcinoma, including carcinoembryonic antigen (CEA), pancreatic anti-oncofetal 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 as well as in 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.[35] Furthermore, a decrease in serial CA 19-9 levels has been found to correlate with survival of pancreatic cancer patients after surgery[36] or chemotherapy.[37,38] However, CA 19-9 may be falsely positive in cases of benign biliary obstruction[39] or falsely negative in Lewis a-negative individuals. Preoperative measurement of cancer antigen (CA) 19-9 levels should be performed after biliary decompression is complete (see PANC-2).

Biopsy

Although a histologic diagnosis is not required before surgery, it is necessary before administration of neoadjuvant therapy. A histologic diagnosis of adenocarcinoma of the pancreas is often made using fine-needle aspiration (FNA) biopsy with either endoscopic ultrasonography (EUS) guidance (preferred) or CT (see PANC-3). EUS-directed FNA biopsy is preferable to CT-guided FNA in patients with resectable disease because of the much lower risk of peritoneal seeding with EUS-FNA when compared with the percutaneous approach.[40] A negative biopsy should be confirmed by at least one repeat EUS biopsy. 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.[22] It can be difficult to discriminate between non-neoplastic and neoplastic cystic pancreatic lesions radiographically; however, EUS-guided FNA of cystic pancreatic lesions can be useful in the differential diagnosis of these lesions.[41] Pancreatic ductal brushings or biopsies can also be obtained at the time of ERCP, often revealing malignant cytology consistent with pancreatic adenocarcinoma. It is important to reiterate that biopsy proof of malignancy 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 NCCN Pancreatic Adenocarcinoma Panel strongly

recommends that all diagnostic and surgical management decisions involve multidisciplinary consultation. Biopsy confirmation of disease is required for patients staged with locally advanced/unresectable disease without evidence of metastases or metastatic disease (see PANC-5; PANC-7; PANC-9). In the case of metastatic disease, percutaneous biopsy from a metastatic site is preferred (see PANC-9).

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 NCCN Pancreatic Cancer Panel is in favor of 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. The CAP protocols comply with the COC requirements, and the latest revisions to the CAP Pancreatic (Exocrine) protocol were issued in January 2005. Therefore, pathologists should familiarize themselves with these documents.

TNM Staging/Clinical Staging

The American Joint Committee on Cancer (AJCC) has developed staging criteria for adenocarcinoma of the pancreas (see Table 1).[42] Recent validation of concordance between AJCC stage and overall survival has been provided through evaluation of 121,713 patients with pancreatic adenocarcinoma included in the National Cancer Database (NCDB).[43] Although the TNM staging criteria for pancreatic cancer in the 6th 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 evaluation of resected tumor.[42] For clinical purposes, most NCCN centers use a clinical staging system based mainly on results of presurgical imaging studies. Following staging by 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 (ie, tumors which are involved with nearby structures so as to be neither clearly resectable nor clearly unresectable); (3) locally advanced unresectable (ie, tumors which are involved with nearby structures to an extent which renders them unresectable despite the absence of evidence of metastatic disease); or (4) disseminated (see section on Criteria for Resection, below), and this is the system used throughout the guidelines. Although not part of the TNM staging system criteria, it is recommended by the AJCC that the surgeon 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; and (3) R2 for incomplete tumor resection with gross residual tumor that was not resected.[42]

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.[44] Early concerns about high mortality associated with various pancreatic resection procedures[45] have now been lessened by studies demonstrating an acceptably low (< 5%) mortality in experienced centers (see below).[46] 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%.[47] Negative margin status (ie, R0 resection), tumor DNA content, tumor size, and

absence of lymph node metastases are the strongest prognostic indicators for long-term patient survival.[48-50] With respect to margin status, there is also evidence for the converse statement – the survival benefits of an R1 resection may be comparable to palliative chemoradiation without surgery.[51]

A review of the biomedical literature indicates that there are no universally accepted criteria for resection. The NCCN Panel therefore recommends that decisions about diagnostic management and resectability always involve multidisciplinary consultation, with appropriate radiographic studies to evaluate the extent of disease. Although it is clear that patients with visceral, peritoneal, pleural metastases, and metastases to nodes beyond the field of resection derive no benefit from resection, institutions appear to differ in their approaches to patients with locoregional (pancreas and peripancreatic lymph node) disease involvement. NCCN surgeons have derived criteria for resectability based on their clinical experience with the primary management of pancreatic tumors. Using these criteria tumors are classified as: resectable; borderline resectable; or unresectable (eg, locally advanced or metastatic disease) (see PANC-B).

The criteria for borderline resectable lesions include superior mesenteric vein (SMV) occlusion of a short segment, with an open vein proximally and distally. However, if the proximal SMV is occluded at its branches in the mesocolon or up to the portal vein branches, then this is considered unresectable. There may be tumors with limited involvement of the inferior vena cava that are borderline resectable. Tumors involving the hepatic artery and celiac axis have been successfully resected in a few specialty centers, but there are not enough data yet to put them in the borderline resectable category. It is important to note that there is no uniform consensus on criteria for defining resectability nor are there good clinical data on this topic. However, the likelihood of attaining negative surgical margins (ie, R0 resection) is a key criterion for consideration when determining whether a patient is a potential candidate for resection.[52,53] In this context, a borderline resectable lesion can be defined as one in which there is a higher likelihood of an incomplete (R1 or R2) resection (see PANC-B).

Primary Surgery for Pancreatic Cancer

The only curative therapy for pancreatic cancer is resection of the tumor and the surrounding pancreatic tissue. The nature and the extent of the surgery 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. Patients with tumors in the head of the pancreas, who usually present because of jaundice, are treated with pancreaticoduodenectomy (the Whipple procedure). This complex procedure has several controversial issues associated with it that are discussed in more detail in the next section.

Preoperative Biliary Drainage

The main goals of preoperative biliary drainage are to alleviate the symptoms of pruritus and cholangitis as well as to potentially make surgery less morbid by improving liver function preoperatively. Although controversial, several studies have suggested that pancreaticoduodenectomy is associated with higher perioperative mortality when done in the setting of hyperbilirubinemia.[54-56] Stenting of the biliary system can improve symptoms and liver function, but it is not clear whether these changes can decrease the mortality rate of the Whipple procedure. Several prospective and retrospective studies have failed to show decreased mortality in patients with preoperative biliary drainage.[57-63] In 1999, a retrospective study from Memorial Sloan-Kettering Cancer Center examined 240 consecutive pancreaticoduodenectomies where 53% of patients underwent preoperative biliary decompression.[64] 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 M. D. Anderson Cancer Center reported on their experience with more than 300 patients of whom 57% had preoperative biliary drainage[65] as part of a neoadjuvant chemoradiation program. It was found that wound complications were significantly increased in the drainage group; however, no other association was found for sepsis, fistulae, or death. Based on these reports, most groups who perform resection first advocate selective use of decompression only in patients who are symptomatic or septic, or in whom surgical resection is significantly delayed. For patients undergoing neoadjuvant induction therapy before pancreatic resection, biliary decompression is necessary to initiate therapy and appears 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 (eg, plastic stent) if symptoms of cholangitis or fever are present (see PANC-2). Endoscopic placement of a temporary stent is recommended prior to CA 19-9 testing during the initial workup of patients with obstructed jaundice characterized by symptoms of cholangitis or fever when there is no evidence of metastatic disease (see PANC-2). A temporary stent is also recommended prior to administration of neoadjuvant therapy for patients with jaundice and borderline resectable disease that is biopsy-positive (see PANC-6).

Pylorus Preservation

Reconstruction options for the stomach after pancreaticoduodenectomy center around preservation of the pylorus. Traverso and Longmire[66] 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 to date. Yeo et al[67] reported no adverse affects of pylorus preservation; however, van Berge Henegouwen et al[68] reported longer nasogastric drainage times. In several randomized and nonrandomized studies,[69-73] 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 potentially 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.[74] 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.[75,76] Although no evidence is convincing that one method of anastomosis is better than another, a study has suggested that meticulous attention to blood supply can help ensure a low rate of anastomotic failure.[77] Stents used in the 1930s and 1940s continue to be used today, but no data suggest that they decrease leak rates.[78] Pancreatic fistula rates are similar (ranging in most studies from 6% to 16%),[67,75,79] although the exact way to define a pancreatic leak in terms of volume and duration of drainage remains controversial.[80]

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 two prospective, randomized, double-blind, placebo-controlled studies (ie, University of Texas M. D. Anderson Cancer Center, Johns Hopkins Hospital).[81,82] Finally, the use of fibrin glue sealant does not appear to decrease the rate of pancreatic fistulas.[83]

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.[84] 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, in the 1990s, there was renewed interest in vein resection for complete resections. The group from Texas (University of Texas M.D. Anderson Cancer Center) has championed this approach, arguing that because overall mortality from pancreaticoduodenectomy has decreased, vein resection and reconstruction allows for complete resection and is not associated with increased morbidity or mortality when compared with patients who did not require vein resection.[85] Furthermore, long-term outcome is not significantly worse.[86] 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 receiving vein resection.[87-90] 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 those having standard pancreaticoduodenectomy and was superior to historical patients believed to have locally advanced disease who did not receive surgical treatment.[91] 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 last 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 demonstrated a high incidence of nodal metastasis (sometimes as high as 80%), leading some groups to propose a more aggressive lymphadenectomy[92,93] in an attempt to regionally control disease. The definition varies of 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 axis.[94]

Several retrospective or single institution nonrandomized studies have looked at the role of extended lymphadenectomy. The most promising results are from Japan, where a few studies reported improved survival in patients who underwent more extensive operations, including lymphadenectomy, although these studies included only a few patients.[95,96] In general, these studies had significant imbalances among patients with regard to stage of disease. In contrast, several additional studies from the United States and Europe have failed to show a survival advantage in patients undergoing regional lymphadenectomy.[97,98]

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 the 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.[99] A larger randomized prospective trial is currently being done at Johns Hopkins Hospital to evaluate the role of extended lymph node dissections.[100] At last update, 299 patients had been 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 two groups at 1, 3, and 5 years.[101]

The information to date 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 as 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. At this point in time, 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 and colleagues[102] assessed 223 pancreaticoduodenectomies from 26 U.S. hospitals, but they found that caseload did not correlate with mortality. However, surgeons who performed fewer than four resections per year had more complications. The group from Memorial Sloan-Kettering Cancer Center 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% versus 12.3%) than low-volume centers.[103] High volume was defined as more than 40 cases per year, and this relationship correlated in a regression analysis. Of note, 75% of the cases in New York State were performed in low-volume centers. Furthermore, regional outcomes with pancreaticoduodenectomy from U.S. hospitals were assessed in several other studies that have also reported decreased mortality, hospital length of stay, and overall cost at higher volume centers when compared with low-volume centers.[104-108] Interestingly, this effect was also seen in reports from Canada and the Netherlands.[109,110]

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/year) and in low-volume (1-2 procedures/year) hospitals are compared with rates in higher-volume hospitals (> 5 procedures/year).[111] 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, versus 4%; $P < 0.001$). The importance of hospital volume in improving survival after pancreatic cancer surgery is even more marked when pancreaticoduodenectomy is compared to other major surgeries. In a retrospective analysis of data from the national Medicare claims database and the Nationwide Inpatient Sample, hospitals performing 6-16 and >16 procedures per year, were classified as “high” and “very-high” volume centers.[112] 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, as compared to major surgery at any other sites, further reinforcing the magnitude of the effect that high-volume centers can specifically have on pancreatic cancer outcomes.[112]

The NCCN Panel recommendation is that pancreatic resections should be done at institutions that perform a large number (>20) of pancreatic resections annually (see PANC-A).

A very recent study involving 301,033 patients with pancreatic adenocarcinoma included in the NCDB evaluated the treatment patterns of 1,667 hospitals over a 19 year period.[113] During that time, the pancreatectomy rate as well as the use of multimodality adjuvant therapy (ie, surgery plus chemoradiation) for patients with stage I and II disease increased significantly (pancreatectomy rate increased from 39.6% to 49.3%, P<0.0001; use of multimodality therapy increased from 26.8% to 38.7%, P<0.0001). Further, patients were more likely to receive 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 1995-2004 revealed that a high percentage of these patients were not treated surgically, and that 38.2% of such patients were not offered this option, despite the fact that it is the only treatment with curative potential.[114] Nevertheless, the consensus of the Panel is that patients should be selected for surgery on the basis of curative intent as determined by the probability of obtaining R0 resection margins. Patients at high risk for positive surgical margins are not considered to be good candidates for an upfront resection.

Adjuvant Therapy

Postoperative Chemoradiation

In 1985, the Gastrointestinal Tumor Study Group (GITSG) initially reported that the median survival of patients undergoing pancreaticoduodenectomy could be prolonged almost 2-fold by postoperative chemoradiation.[115] In this study, patients were randomly assigned to either observation or radiation therapy (RT) combined with an intermittent bolus of 5-fluorouracil (5-FU) after resection. A standard split course of 4,000 cGy was used. 5-FU, 500 mg/m^2 daily for 3 days, was given concurrently with each 2,000-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.

The European Organization for Research and Treatment of Cancer (EORTC) conducted a phase III trial assessing adjuvant radiotherapy and 5-FU versus observation alone after surgery; however, they found the benefit of therapy was small in a subset of patients with pancreatic adenocarcinoma and was not statistically significant.[116]

Provocative but controversial results from the European Study Group for Pancreatic Cancer (ESPAC)-1 trial have been reported by Neoptolemos and colleagues.[117] Results of this study suggested that 5-FU 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 as well as for lack of attention to quality control for RT.[118,119] Therefore, these latest results do not eliminate 5-FU--based chemoradiation as an acceptable choice in the adjuvant setting.

Recently, results from the large phase III CONKO-001 trial in which 368 patients without prior chemotherapy or radiation therapy were randomly assigned to adjuvant gemcitabine versus observation following

macroscopically complete resection showed that disease-free survival was significantly increased in the patients who received gemcitabine (13.4 months vs. 6.9 months; P<0.001), and this benefit was observed in patients with R0 and R1 resections.[120] However, no differences in median overall survival were observed in the 2 groups by intention-to-treat analysis (22.1 months in the gemcitabine arm and 20.2 months in the control group (P=0.061, log-rank). Nevertheless, the results of the CONKO-001 trial provide support for the use of postoperative gemcitabine as adjuvant therapy.

Very recently, the Radiation Therapy Oncology Group (RTOG) has conducted a phase III study (RTOG 97-04) assessing pre- and post-chemoradiation 5-FU versus pre- and post-chemoradiation gemcitabine for postoperative adjuvant treatment of resected pancreatic adenocarcinoma.[121] This trial which utilized daily fractionated radiotherapy included prospective quality assurance of all patients, including central review of preoperative CT imaging and radiation fields.[122] Results of this study showed that, for patients with tumors of the pancreas head (representing 380 of the 442 patients enrolled in the trial), overall survival was significantly increased in the gemcitabine arm compared with the 5-FU arm (median and 3-year survival of 20.6 months and 32% vs. 16.9 months and 21%; P=0.047; hazard ratio=0.79, 95% CI=0.63-0.99). However, when all patients in the study were included in this early evaluation, no significant survival differences were observed.

Other evidence for a survival benefit of adjuvant chemoradiation over observation comes from 2 population-based studies – one at a single institution and the other using the Surveillance, Epidemiology, and End Results (SEER) database.[123,124]

Results of RTOG 97-04 cannot be directly compared with the results of either the CONKO-001 trial or the ESPAC-1 trial because of differences in treatment design as well as fundamental differences in patient characteristics (eg, patients enrolled in CONKO-001 were more likely to be lymph node-negative and to have positive resection margins than those in RTOG 97-04). However, it is interesting to note that median overall survival for patients in the gemcitabine arm of CONKO-001 (22.1 months), the gemcitabine-containing arm of RTOG 9704 (20.6 months for patients with pancreatic head tumors), and the bolus 5-FU arm of ESPAC-1 (20.1 months) was remarkably similar. Therefore, at this time, no definite standard has been established in the adjuvant treatment of pancreatic cancer and both 5-FU-based chemoradiation with additional gemcitabine-chemotherapy, as well as chemotherapy alone with gemcitabine, 5-FU, or capecitabine are listed in the guidelines as options for adjuvant treatment. All of these adjuvant therapy options are designated as category 2A recommendations. However, it was the consensus of the Panel that when chemotherapy alone is the choice of adjuvant therapy, gemcitabine is preferred over either 5-FU or capecitabine for most patients, and that systemic gemcitabine should be administered with adjuvant 5-FU-based chemoradiation when chemoradiation is the adjuvant therapy choice. Whereas results from the RTOG trial suggest an advantage for adjuvant therapy with gemcitabine over infusional 5-FU, the prospective randomized trial of bolus 5-FU/leucovorin versus gemcitabine versus observation following surgery (ESPAC-3), which is in progress, should provide more definitive results of the use of chemotherapy without chemoradiation after surgery. Nevertheless, with the emergence of new agents to treat pancreatic cancer, particularly biologics, adjuvant clinical trials designed to incorporate principles of molecular biology and new imaging methods may be more beneficial than those focused on a comparison of chemotherapy versus chemoradiation.[125]

Although the optimal combination and sequencing of RT has yet to be defined, the NCCN Panel recommends that postoperative RT, when given, should be administered at a dose of 45 to 54 Gy (1.8-2.0 Gy/day) (see PANC-C).[126] Use of CT simulation and 3D 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 with systemic gemcitabine in the adjuvant setting (see PANC-4). Emerging data in the study of locally advanced disease suggest that a period of chemotherapy followed by consolidated chemoradiation may be preferable to upfront chemoradiation.[127,128] Therefore, the Panel recommends that when chemoradiation is considered as adjuvant therapy, it should be administered following an adequate course of systemic chemotherapy (eg, as described by the RTOG 97-04 protocol).[121]

Adjuvant chemotherapy or adjuvant chemoradiation should only be considered for patients who have adequately recovered from surgery; treatment should ideally be initiated within 4 to 8 weeks (see PANC-4). It is recommended that the patient undergo a baseline assessment, including CT scan (category 2B) and CA 19-9 level, following surgery to evaluate for the presence of metastatic disease before adjuvant chemoradiation is initiated. Further, the Panel recommends that consideration be given to restaging a patient with a CT scan following systemic chemotherapy, if it will precede chemoradiation (see PANC-4). Adjuvant therapy is not restricted to patients who have not had neoadjuvant therapy but adjuvant chemoradiation should not be administered to patients who have received neoadjuvant chemoradiation.

Preoperative (Neoadjuvant) Therapy

Novel contemporary approaches to adjuvant therapy have focused on preoperative (neoadjuvant) therapy with the goal of improving overall survival.[129,130] A number of studies have investigated the use of neoadjuvant chemoradiation in patients with resectable disease.[25,26,131-133] To date, however, no randomized trials have addressed this issue. A retrospective review of the collective experience at M. D. Anderson Cancer Center indicated that the use of preoperative chemoradiation therapy in patients with resectable disease does not appear 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.[133] Other putative advantages to administering neoadjuvant therapy include: the potential to select for surgery those patients with more stable disease or disease which is more responsive to therapy; treatment of tissue which 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 so as to increase the likelihood of a margin-free resection.[52,130,134] In an analysis of 132 consecutive patients, the M. D. Anderson Cancer Center 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.[132]

Some studies have addressed the use of preoperative chemoradiation therapy to convert selected patients with unresectable disease to a resectable status.[130,131,134-139] Although emerging evidence suggests that there is a better chance of margin-negative resection with preoperative therapy,[140] results of randomized trials involving a clinical end point of R0 resection rate have yet to be reported. Further, the optimal neoadjuvant regimen has not been established. The ongoing phase II Eastern Cooperative Oncology Group (ECOG) 1200 trial is prospectively evaluating the percentage of margin-free resections in patients with potentially resectable pancreatic adenocarcinoma treated with concurrent gemcitabine/RT followed by postoperative gemcitabine versus gemcitabine, 5-FU, and cisplatin followed by 5-FU/RT and postoperative gemcitabine. In addition, the Interdisciplinary Study

Group of Gastrointestinal Tumours of the German Cancer Aid have initiated a prospective, randomized study of neoadjuvant chemoradiation (gemcitabine/cisplatin/RT) versus upfront resection for patients with resectable or potentially resectable disease.[141] Other ongoing trials are evaluating the safety and efficacy of gemcitabine-based chemotherapy regimens as neoadjuvant therapy for patients with potentially resectable pancreatic cancer.[142]

The majority of NCCN centers prefer an initial approach involving neoadjuvant therapy (ie, neoadjuvant chemoradiation), as opposed to upfront surgery, for patients with borderline resectable disease, and the Panel recommends that patients be considered for neoadjuvant therapy following clinical staging of disease as borderline resectable (see PANC-3; PANC-6). Since not all NCCN centers administer neoadjuvant therapy to patients with borderline resectable disease, this recommendation is designated category 2B. EUS-directed biopsy is the preferred method of obtaining histological confirmation of disease in these patients, and such confirmation is necessary before administering neoadjuvant chemoradiation. A repeat biopsy should be performed in cases where the initial biopsy results are negative. A staging laparoscopy, performed to evaluate for the possible presence of metastatic disease, is also recommended (category 2B). Placement of a temporary stent is recommended prior to initiation of neoadjuvant chemoradiation in patients with jaundice (PANC-6). Neoadjuvant chemoradiation regimens are the same as those used to treat locally advanced disease (see section on Chemoradiation for Locally Advanced Disease - below).

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 PANC-3; PANC-6). However, the Panel does not support 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 PANC-5; PANC-8; PANC-C), although the utility of chemoradiation in this population of patients is controversial.[143] The role of chemoradiation was initially defined in a trial conducted by GITSG.[144] In this study, the combination of bolus 5-FU and split-course radiation (total dose, 4,000 cGy) was compared with radiation alone or with 6,000 cGy combined with 5-FU. A nearly twofold increase in median survival (42.2 versus 22.9 weeks) was observed with the regimen of bolus 5-FU and 4,000 cGy 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, the NCCN recommends doses of 50 to 60 Gy (1.8-2.0 Gy/day) with concomitant 5-FU (see PANC-C).[126,145] Use of CT simulation and 3D 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, 5-FU--based chemoradiation therapy is recommended for patients with unresectable disease, no metastases, and good performance status.

Other radiation sensitizers under study include bromodeoxyuridine,[146] paclitaxel,[147] cisplatin,[148] and gemcitabine.[149,150] There is evidence to suggest that concurrent gemcitabine and radiation can yield similar outcomes when compared with 5-FU--based chemoradiation,[151] 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 (NCCTG) 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.[152] 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 PANC-5; PANC-8). The Panel recommends that additional systemic chemotherapy (gemcitabine-based) be considered for patients with locally advanced disease who are receiving chemoradiation therapy. Further, emerging data suggest that a period of chemotherapy followed by consolidated chemoradiation may be preferable to upfront chemoradiation.[127,128] For example, a retrospective analysis of outcome from the 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.[127] When systemic chemotherapy precedes administration of chemoradiation, the Panel recommends restaging with a CT scan prior to RT.

Chemotherapy without RT is also an option for patients with locally advanced pancreatic cancer (see PANC-5; PANC-8; PANC-D). Results of 2 early randomized trials comparing chemoradiation to chemotherapy in locally advanced disease were contradictory.[153,154] Gemcitabine alone (without radiation) or gemcitabine-based combination therapy (see Role of Gemcitabine and Gemcitabine Combinations) is an alternative to 5-FU--based chemoradiation. A phase III randomized trial (ECOG-4201) was in progress to assess gemcitabine compared with gemcitabine plus 5-FU/RT in patients with locally advanced, unresectable pancreatic cancer but it was closed early due to poor accrual. 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 induction treatment followed by maintenance treatment with gemcitabine or chemoradiation with 5-FU plus cisplatin followed by gemcitabine maintenance treatment.[155] In this study, gemcitabine alone was associated with a significantly increased overall survival rate at 12 months compared with chemoradiation. Patients in the chemoradiation arm experienced increased toxicity and were more likely to receive 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. This study was stopped before the planned inclusion.

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 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's Supportive Care Guidelines). Before initiating cytotoxic therapy, an open dialogue regarding the goals of treatment should take place, and adjunctive strategies should be discussed (including nonsurgical bypass, celiac block for pain; see Palliation of locally advanced and metastatic disease, and PANC-E). Of note, 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.[156] The NCCN Panel recommends gemcitabine monotherapy (1,000 mg/m^2 over 30 min, weekly for 3 weeks every 28 days) as standard front-line therapy for patients with metastatic disease (category 1) (see PANC-8; PANC-9; PANC-D).[156] The NCCN Panel also debated whether gemcitabine monotherapy should be recommended for patients with unresectable, locoregional disease. Because the approved indications for gemcitabine include the relief of symptoms, 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) or best supportive care (see NCCN Supportive Care Guidelines) (see PANC-5; PANC-8). For patients who derive clinical benefit from initial gemcitabine treatment in the setting of locally advanced disease, without developing distant disease, subsequent fluorinated pyrimidine-based therapy may enhance local control (category 2B) (see Second-Line Therapy).

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/minute) maximizes intracellular concentrations of the phosphorylated forms of gemcitabine.[157] In a randomized phase II trial, the infusion of gemcitabine at a FDR led to a higher response rate and better survival compared with gemcitabine delivered at a higher dose, over 30 minutes.[158] The NCCN Panel acknowledged an increasing tendency among clinicians to deliver gemcitabine at FDR. In addition, FDR gemcitabine is being further investigated in the context of ongoing clinical trials in advanced pancreatic cancer. When gemcitabine is considered for the treatment of advanced pancreatic cancer, the NCCN Panel views FDR gemcitabine (10 mg/m^2/minute) as a reasonable alternative to the standard infusion of gemcitabine over 30 minutes (category 2B).

Gemcitabine Combinations

The NCCN Panel also acknowledged that, historically, combination chemotherapy has not appeared to be superior to monotherapy 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. The ECOG has compared gemcitabine monotherapy with gemcitabine and bolus 5-FU in patients with advanced pancreatic cancer; no statistically significant survival advantage was observed for patients receiving the combination regimen.[159] Gemcitabine (standard or FDR infusion) has also been investigated in combination with potentially synergistic agents (such as cisplatin, oxaliplatin, capecitabine, and irinotecan) or in a multidrug combination (eg, cisplatin, epirubicin, gemcitabine, and 5-FU [PEFG]).[160-164] With the exception of gemcitabine plus irinotecan, all of these studies showed a favorable impact on time to progression or survival. A recent randomized phase III trial evaluating gemcitabine with or without cisplatin in patients with advanced pancreatic cancer demonstrated a trend toward increased

overall survival and progression-free survival in the combination arm relative to the control arm but these differences were not statistically significant.[164] A randomized study in 533 patients with advanced or metastatic cancer found that overall survival and objective response rates were significantly improved in patients receiving gemcitabine plus capecitabine when compared with gemcitabine alone,[163] However, results from another smaller phase III trial evaluating this combination did not support this conclusion for the overall study population, although overall survival was significantly increased in the subgroup of patients with good performance status.[165] Of note, results from several studies have indicated that the benefit of gemcitabine combination chemotherapy is predominantly seen in patients with good performance status.[165-167] The NCCN Panel considers gemcitabine-based combination therapy with cisplatin or fluoropyrimidines to be a reasonable option for patients with locally advanced or metastatic disease and a good performance status (category 2A) (see PANC-5; PANC-8; PANC-9) who are interested in pursuing more aggressive therapy outside a clinical trial. At the 2006 American Society of Clinical Oncology (ASCO) meeting, the ECOG presented results from a large randomized trial comparing standard-infusion gemcitabine to either FDR gemcitabine or gemcitabine plus oxaliplatin; this trial showed that all three arms were equivalent for overall survival.[168]

Although phase II trial results of gemcitabine combined with new targeted drugs (eg, bevacizumab, cetuximab or erlotinib) have been encouraging,[169,170] results of phase III studies of these combinations have indicated that only the combination of gemcitabine plus erlotinib is associated with a statistically significant increase in survival when compared to gemcitabine alone.. Results of the Cancer and Leukemia Group B (CALGB) phase III trial which evaluated gemcitabine and bevacizumab (which is an anti-VEGF [vascular endothelial growth factor] antibody) compared with gemcitabine plus placebo in patients with locally advanced or metastatic pancreatic cancer and the Southwest Oncology Group (SWOG) phase III randomized trial which assessed cetuximab (which targets the epidermal growth factor receptor [EGFR]) plus gemcitabine versus gemcitabine alone did not reveal improvements in survival upon addition of the biologic agent.[171,172] However, in a phase III trial of patients (n = 569) with advanced or metastatic pancreatic cancer randomly assigned to receive erlotinib (which is an inhibitor of EGFR tyrosine kinase) plus gemcitabine versus gemcitabine alone, patients in the erlotinib arm showed statistically significant improvements in overall survival (hazard ratio=0.82; P=0.038) and progression-free survival (hazard ratio=0.77; P=0.004) when compared to patients receiving gemcitabine alone. Median survival was 6.24 months and 1-year survival was 23% compared with 5.91 months and 17% in the control arm.[173] Adverse events, such as rash and diarrhea, were increased in the group receiving erlotinib. The Food and Drug Administration (FDA) recently approved erlotinib in combination with gemcitabine for first-line treatment of patients with locally advanced unresectable or metastatic pancreatic cancer. The NCCN Panel recommends gemcitabine-erlotinib combination therapy as an option for patients with locally advanced or metastatic disease and good performance status (category 2A) (see PANC-5; PANC-8; PANC-9).

Other non-cross-resistant drug combinations are being explored. A phase II study found that the combination of docetaxel and irinotecan was useful in patients (n = 37) with unresectable or metastatic pancreatic cancer.[174] Recently, the median overall survival of patients with advanced pancreatic cancer randomly assigned to receive irinotecan/docetaxel with and without cetuximab was reported to be 6.5 and 7.4 months, respectively.[175] In a single arm phase II trial of patients with advanced pancreatic cancer receiving irinotecan/docetaxel, a median survival of 9.4 months was reported.[176] A randomized phase II trial of three different regimens in patients with advanced pancreatic cancer is currently in progress and interim results suggest that a

capecitabine plus oxaliplatin regimen is comparable to gemcitabine combined with either capecitabine or oxaliplatin.[177]

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. Such patients may initially benefit from gemcitabine-based therapy or from investigational therapy. However, these patients will ultimately progress, and a subset of them will continue to have sufficiently good performance status to consider second-line therapy. There is no consensus on second-line therapy for patients with refractory disease. Gemcitabine may offer palliative benefits in the second-line setting if patients have not been previously treated with gemcitabine,[178] although results from a phase II study (n = 30) suggest that FDR gemcitabine and oxaliplatin may be useful in patients who have become refractory to standard gemcitabine therapy.[179] At present, however, it is unclear whether this benefit is related to the addition of oxaliplatin or the delivery of gemcitabine by the FDR method. For patients who have received prior gemcitabine-based therapy, the NCCN Panel encourages treatment in a clinical trial. However, when investigational therapy is not available, treatment options include capecitabine with or without oxaliplatin or 5-FU plus oxaliplatin (all category 2B) (see PANC-5; PANC-8; PANC-9; PANC-D).[180-183] Note that the capecitabine dose (1,000 mg/m^2 PO twice daily) recommended in the algorithms (see PANC-D) is less than the dose described by Cartwright and colleagues, because the higher dose has been associated with increased toxicity (eg, diarrhea, hand and foot syndrome).[182] The phase III CONKO 003 trial is currently evaluating treatment with 5-FU/leucovorin versus 5-FU/leucovorin plus oxaliplatin in patients with advanced pancreatic cancer refractory to gemcitabine.[184]

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 due to biliary obstruction, gastric outlet obstruction, and cancer-related pain is of primary importance (see Principles of Palliation and Supportive Care [PANC-E]).

Biliary obstruction

Approximately 65%-75% of patients with pancreatic cancer develop symptomatic biliary obstruction.[185] 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 (see PANC-8). 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 (ie, 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 randomly 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=0.002), respectively.[186] This conclusion is supported by results of a metaanalysis 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 (RR = 0.52, 95% CI 0.39 - 0.69), although no significant differences in technical/therapeutic success, complications, or 30-day mortality were found.[187]

When a biliary stent cannot be placed (often because the endoscope cannot be advanced passed 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.[188] Durable palliation of biliary obstruction can often be achieved with an expandable metallic biliary endoprosthesis (eg, Wallstent, Boston Scientific).[188]

For patients with jaundice and potentially resectable disease who are found to have unresectable tumors following 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 PANC-6; PANC-E). 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) since choledochojejunostomy/hepaticojejunostomy provides more durable and reliable palliation of biliary obstruction.[185]

Gastric outlet obstruction

Symptomatic gastric outlet obstruction occurs in 10%-25% of patients with pancreatic cancer.[185] 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.[188] An alternative for these patients is percutaneous endoscopic gastrostomy (PEG) tube placement. For a fit patient with a life expectancy greater than 3-6 months (ie, locally advanced disease), a laparoscopic gastrojejunostomy with or without a jejunostomy (J) tube should be considered since it may provide more durable and effective palliation of gastric outlet obstruction than and enteral stent. Nevertheless, placement of an enteral stent is also an option for these patients (see PANC-E).

For 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 in otherwise asymptomatic patients who are found to be unresectable at the time of laparotomy has been evaluated. Two randomized controlled trials have investigated the role of prophylactic gastrojejunostomy for unresectable periampullary cancer – the majority arising from the head of the pancreas.[189,190] 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 reveals 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.[191] General principles for cancer-related pain management can be found in the NCCN Adult Cancer Pain Guidelines. 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.[191,192] Minimally invasive techniques include EUS-guided and percutaneous fluoroscopic- or CT-guided celiac plexus neurolysis (see PANC-E), 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.

Additional palliative interventions

Pancreatic insufficiency

Exocrine enzyme insufficiency in pancreatic cancer is caused by tumor-induced damage to the pancreatic parenchyma and/or the pancreatic duct, as well as surgical removal of pancreatic tissue.[193,194] Oral pancreatic exocrine enzyme replacement therapy is recommended for patients with pancreatic cancer who have symptoms of exocrine enzyme deficiency (eg, steatorrhea) (see PANC-E).

Treatment of thromboembolic disease

The risk of developing venous thromboembolic disease is substantially increased in patients with pancreatic cancer.[195] 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 PANC-E). This recommendation is based on results of the CLOT trial which showed an approximately 2-fold decrease in the incidence of recurrent VTE at 6 months 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.[196]

Depression, pain, malnutrition

The Panel recommends that patients with locally-advanced or metastatic pancreatic cancer receive a formal evaluation by a Palliative Medicine Service, when appropriate (see PANC-E). Additional resources are detailed in the NCCN Palliative Care Guidelines; NCCN Adult Cancer Pain Guidelines; and the NCCN Distress Management Guidelines).

Surveillance

Although data on the role of surveillance in patients with resected pancreatic adenocarcinoma are very 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 history and physical examination for symptom assessment every 3-6 months for 2 years (see PANC-4). 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 although consensus was not uniform on whether this was appropriate (ie, these recommendations are category 2B), because data are not available to show that earlier treatment of recurrences, following detection by increased tumor marker levels or CT scan, leads to better patient outcomes.

Summary

Overall, in view of the poor outcome of patients with all stages of pancreatic cancer, the NCCN 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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