National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Pancreatic Adenocarcinoma

V.2.2010

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Discussion

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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

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Summary of changes in the 2.2010 version of the Pancreatic Adenocarcinoma guidelines from the 1.2010 version include:

Discussion section

- **The Discussion section has been updated to reflect the changes in the 2010 algorithm.**

Summary of changes in the 1.2010 version of the Pancreatic Adenocarcinoma guidelines from the 1.2009 version include:

General

- **Consolidated and reformatted pages of the Guidelines for consistency and presentation.**

PANC-1

- **Following no mass in pancreas on imaging, no metastatic disease added MRI/MRCP as an acceptable study equivalent to EUS/ERCP.**

PANC-2

- **Revised footnote "a": "CA 19-9 may be elevated in cases of benign biliary obstruction and does not represent an appropriate baseline until the patient is decompressed. In addition, CA 19-9 may be undetectable in Lewis-a negative individuals."**

PANC-3

- **Added footnote "f" to unresectable at surgery: "See Principles of Palliation and Supportive Care."**

PANC-4

- **Changed candidate for neoadjuvant therapy to "Planned neoadjuvant therapy"**
- **Added footnote "g": "Most NCCN institutions prefer neoadjuvant therapy in the setting of borderline resectable disease at a high volume center. Performing surgery with a high likelihood of a positive margin is not recommended.**

PANC-5

- **Added a pathway for Disease progression precluding surgery with footnote "f" "Principles of Palliation and Supportive Care."**
- **Planned neoadjuvant therapy, biopsy negative: deleted footnote stating "A negative biopsy should be repeated by EUS at least once more." Added pathway for repeat biopsy to the body of the algorithm. (also added on PANC-6)**

PANC-7

- **Added leucovorin to 5-FU chemotherapy.**
- **Added category 2B designation to capecitabine.**

PANC-11

- **Added "Consider chemical neurolysis and/or chemoradiation."**

PANC-A

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

PANC-B

- **Revised Criteria Defining Resectability Status based on the following reference: Callery M, Chang K, Fishman EK, et al. Pretreatment Assessment of Resectable and Borderline Resectable Pancreatic Cancer: Expert Consensus Statement. Ann Surg Oncol 2009;16:1727-1733.**

PANC-C

- **Under severe tumor-associated abdominal pain, added a new bullet "Consider palliative chemoradiation if not already given as part of primary therapy regimen."**

PANC-E (1 of 2)

- **Changed the format according to therapy for: metastatic, locally advanced and adjuvant**
- **Under metastatic, added fixed dose rate gemcitabine + oxaliplatin.**
- **Under adjuvant therapy added a bullet: "ESPAC-3 study results showed no significant difference in overall survival between 5FU/leucovorin versus gemcitabine following surgery. When the groups receiving adjuvant 5-FU/leucovorin and adjuvant gemcitabine were compared median survival was 23.0 months and 23.6 months, respectively."**
- **Also added reference 8: Neoptolemos J, Buchler M, Stocken DD, et al. ESPAC-3 (2): A multicenter, international, open-label, randomized, controlled phase III trial of adjuvant 5-fluorouracil/folinic acid versus gemcitabine in patients with resected pancreatic ductal adenocarcinoma [abstract]. J Clin Oncol. 2009a;27: 18s (suppl; LBA4505).**

STAGING

- **Updated staging using AJCC Cancer Staging Manual, Seventh Edition (2010).**

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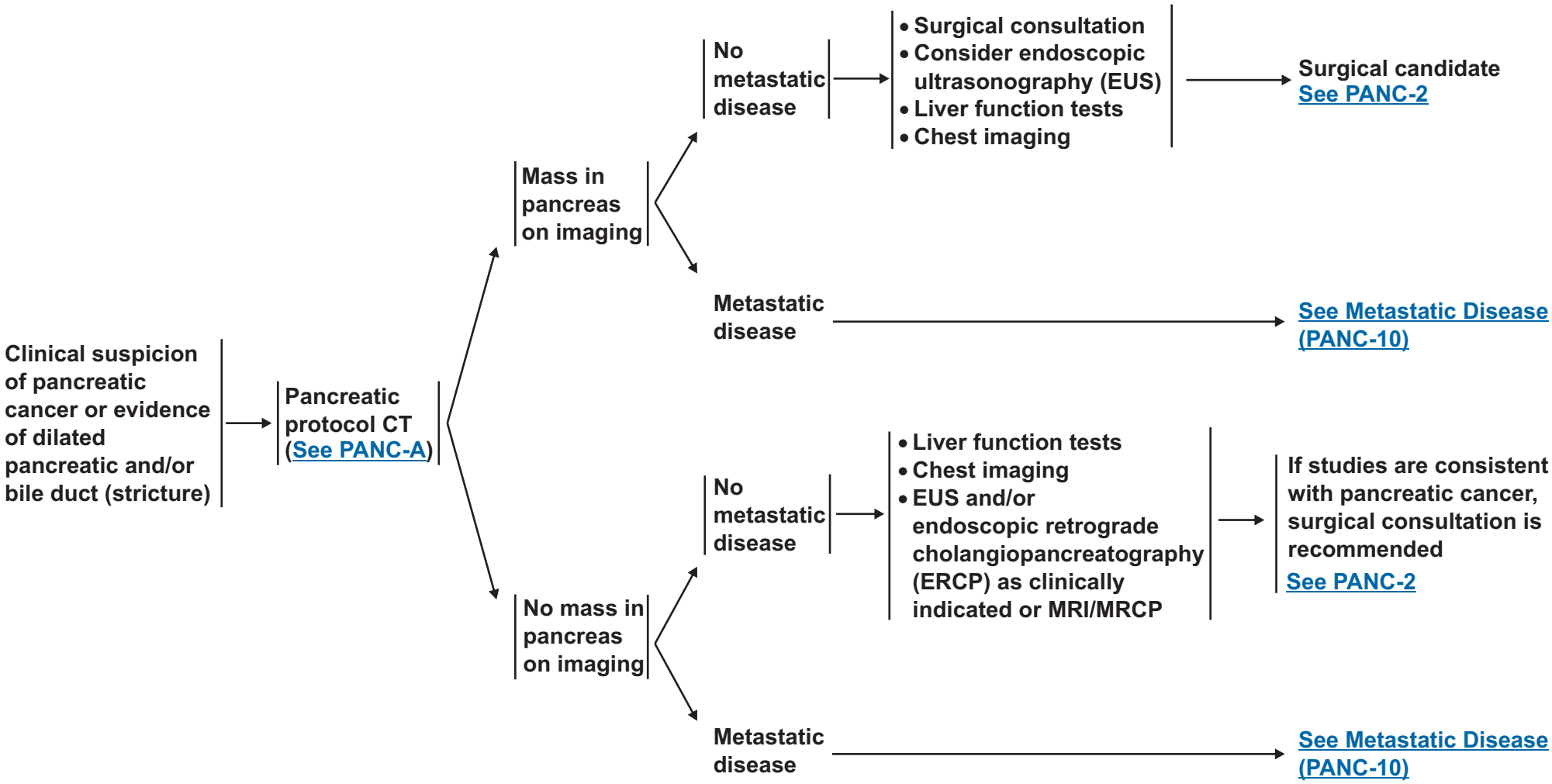
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CLINICAL PRESENTATION

WORKUP



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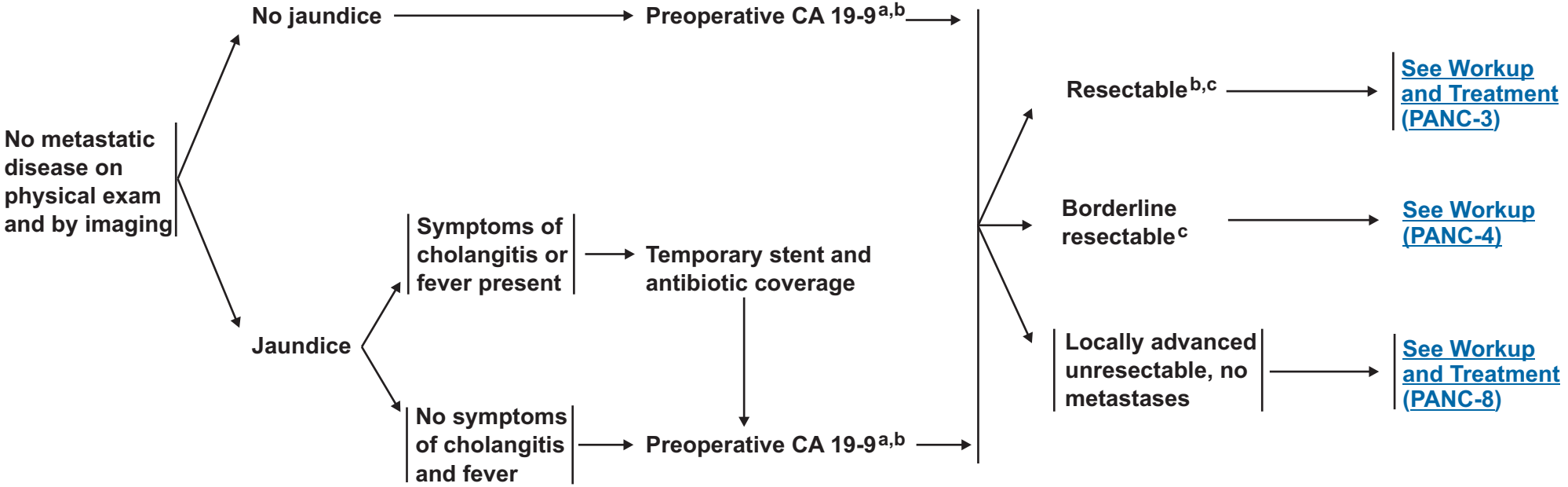
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[a] CA 19-9 may be elevated in cases of benign biliary obstruction and does not represent an appropriate baseline until the patient is decompressed. In addition, CA19-9 may be undetectable in Lewis-a negative individuals.

[b] See Principles of Diagnosis and Staging (PANC-A).

[c] See Criteria Defining Resectability Status (PANC-B).

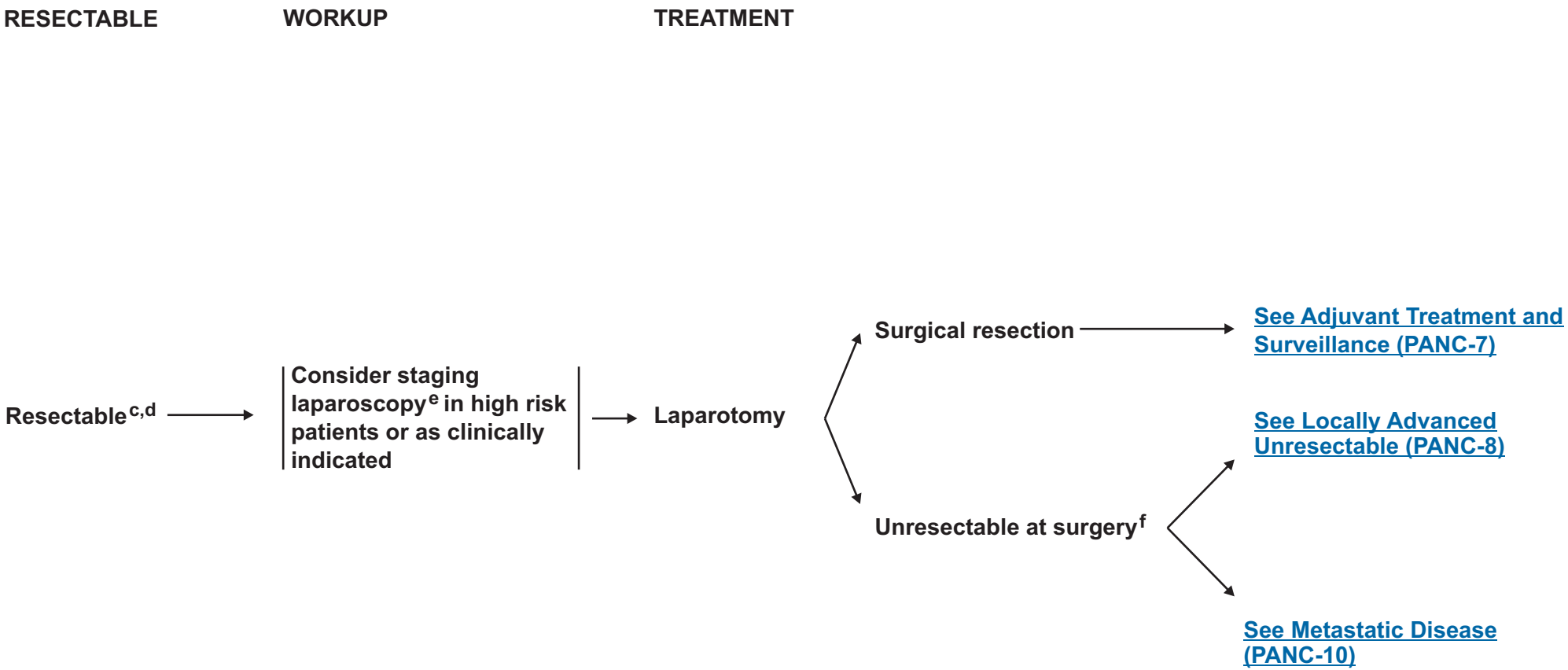
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[c] See Criteria Defining Resectability Status (PANC-B).
[d] Consider neoadjuvant therapy on clinical trial.
[e] See Principles of Diagnosis and Staging #6 (PANC-A).
[f] See Principles of Palliation and Supportive Care (PANC-C).

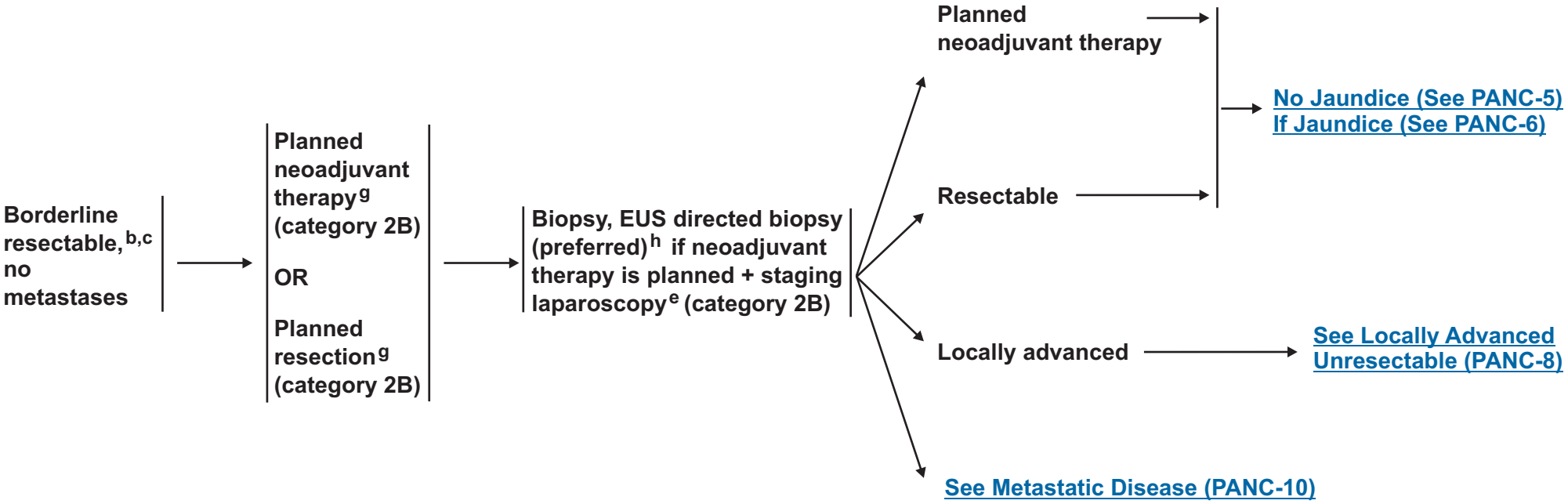
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BORDERLINE RESECTABLE, NO METASTASES

WORKUP



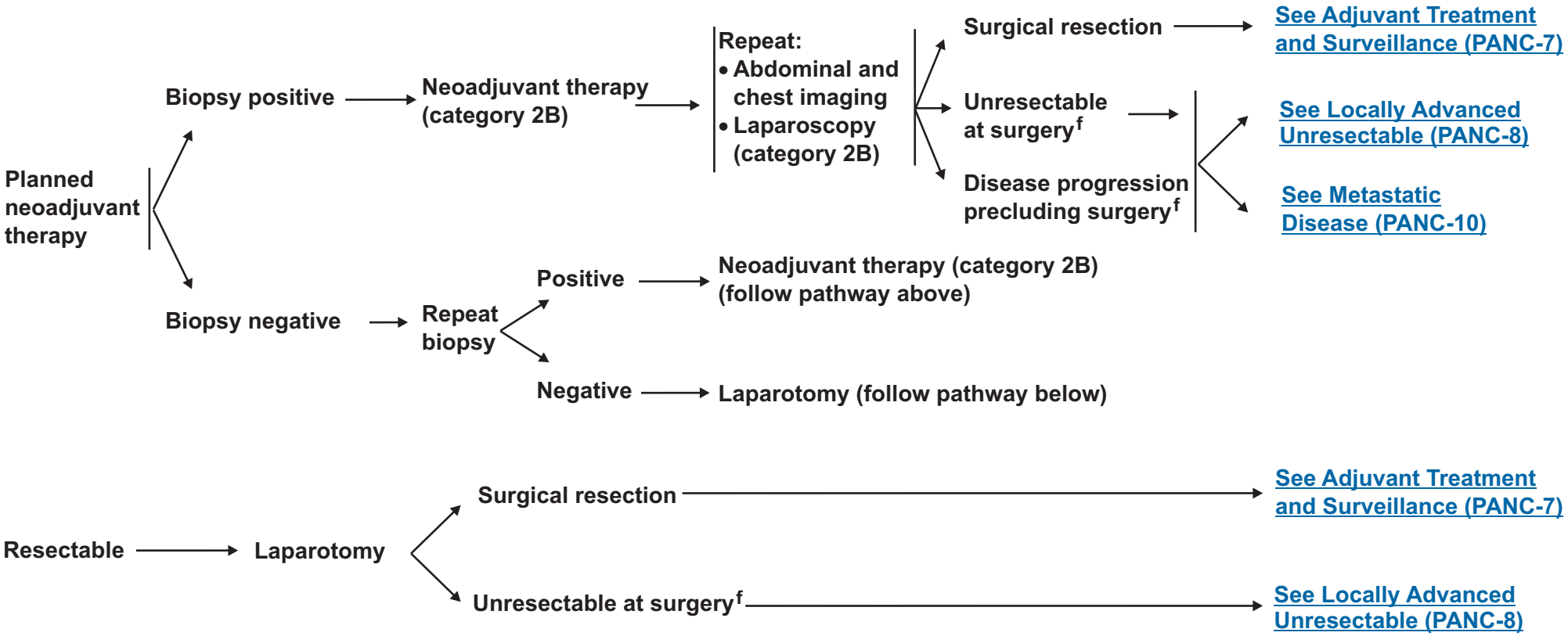
[b] See Principles of Diagnosis and Staging (PANC-A).
[c] See Criteria Defining Resectability Status (PANC-B).
[e] See Principles of Diagnosis and Staging #6 (PANC-A).
[g] Most NCCN institutions prefer neoadjuvant therapy in the setting of borderline resectable disease at a high volume center. Performing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

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BORDERLINE RESECTABLE
NO METASTASES, NO JAUNDICE

TREATMENT



[f] See Principles of Palliation and Supportive Care (PANC-C).

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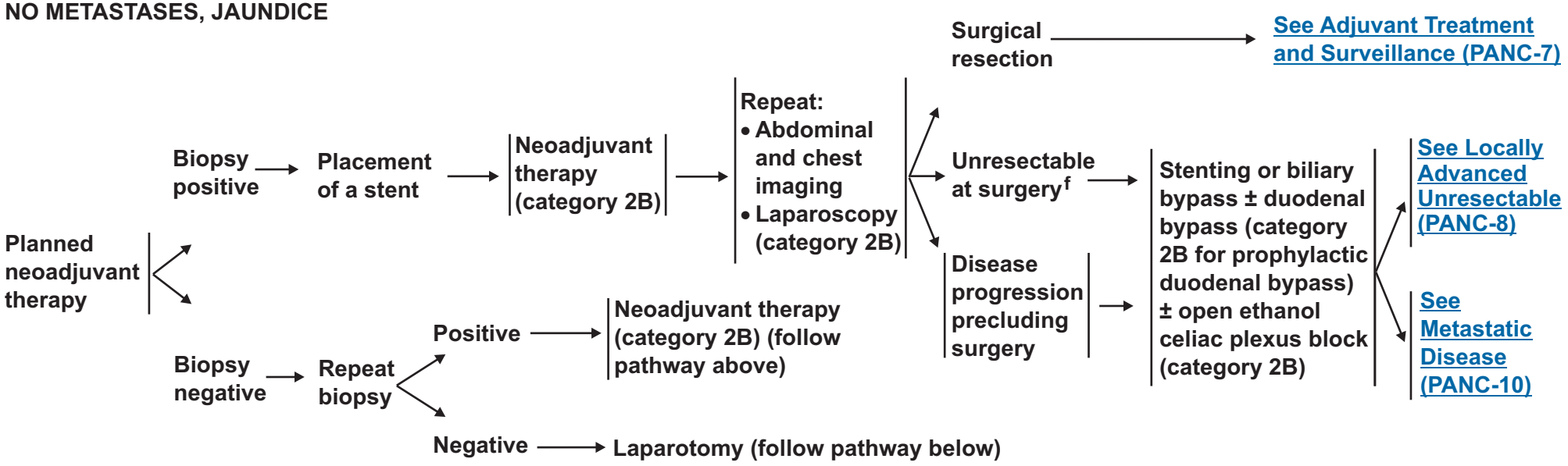
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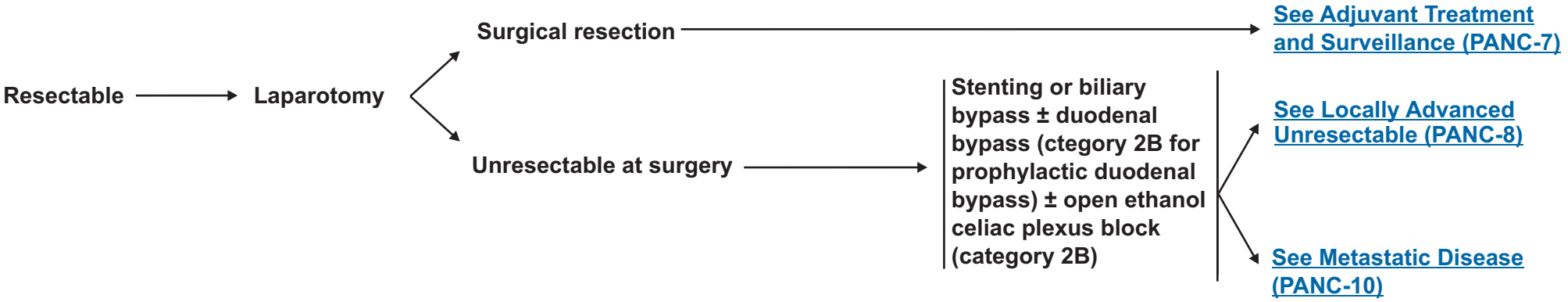
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BORDERLINE RESECTABLE NO METASTASES, JAUNDICE

TREATMENT



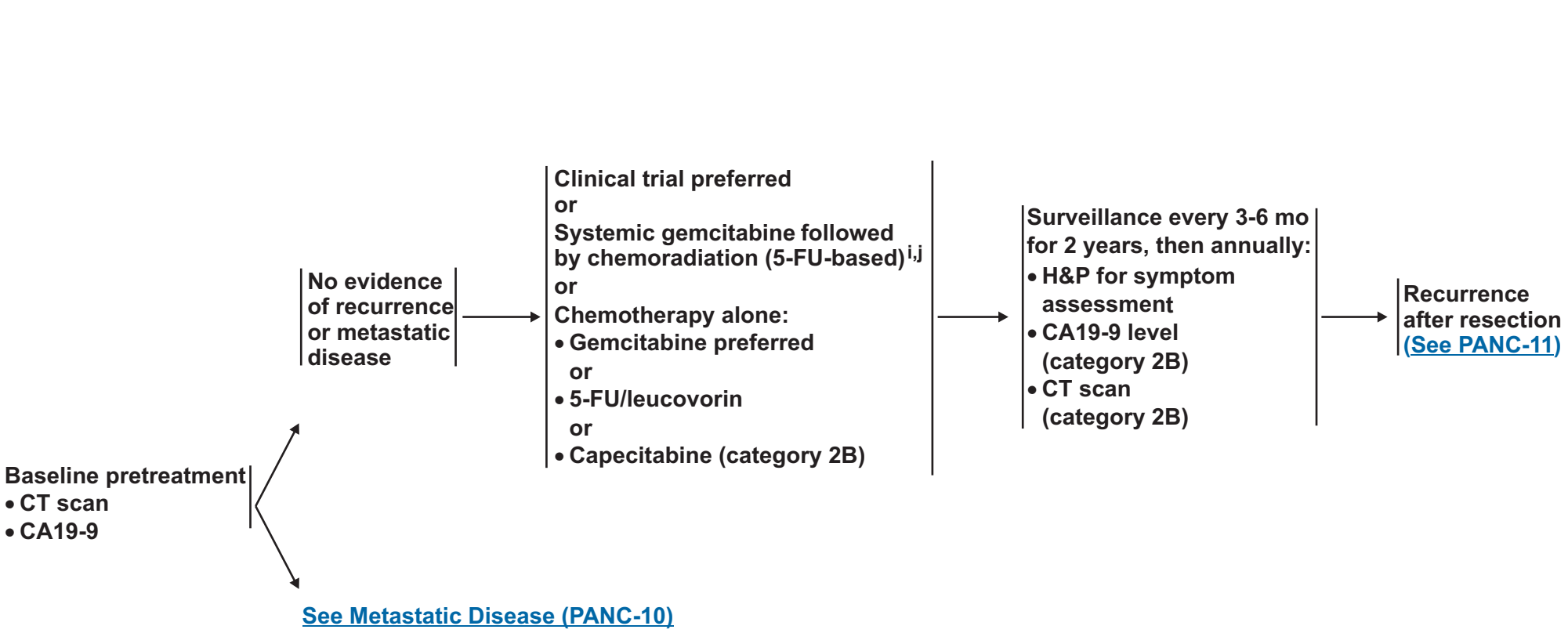


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[i] Adjuvant treatment should be administered to patients who have not had neoadjuvant therapy and who have adequately recovered from surgery; treatment should be initiated within 4-8 weeks. If systemic chemotherapy precedes chemoradiation, restaging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

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

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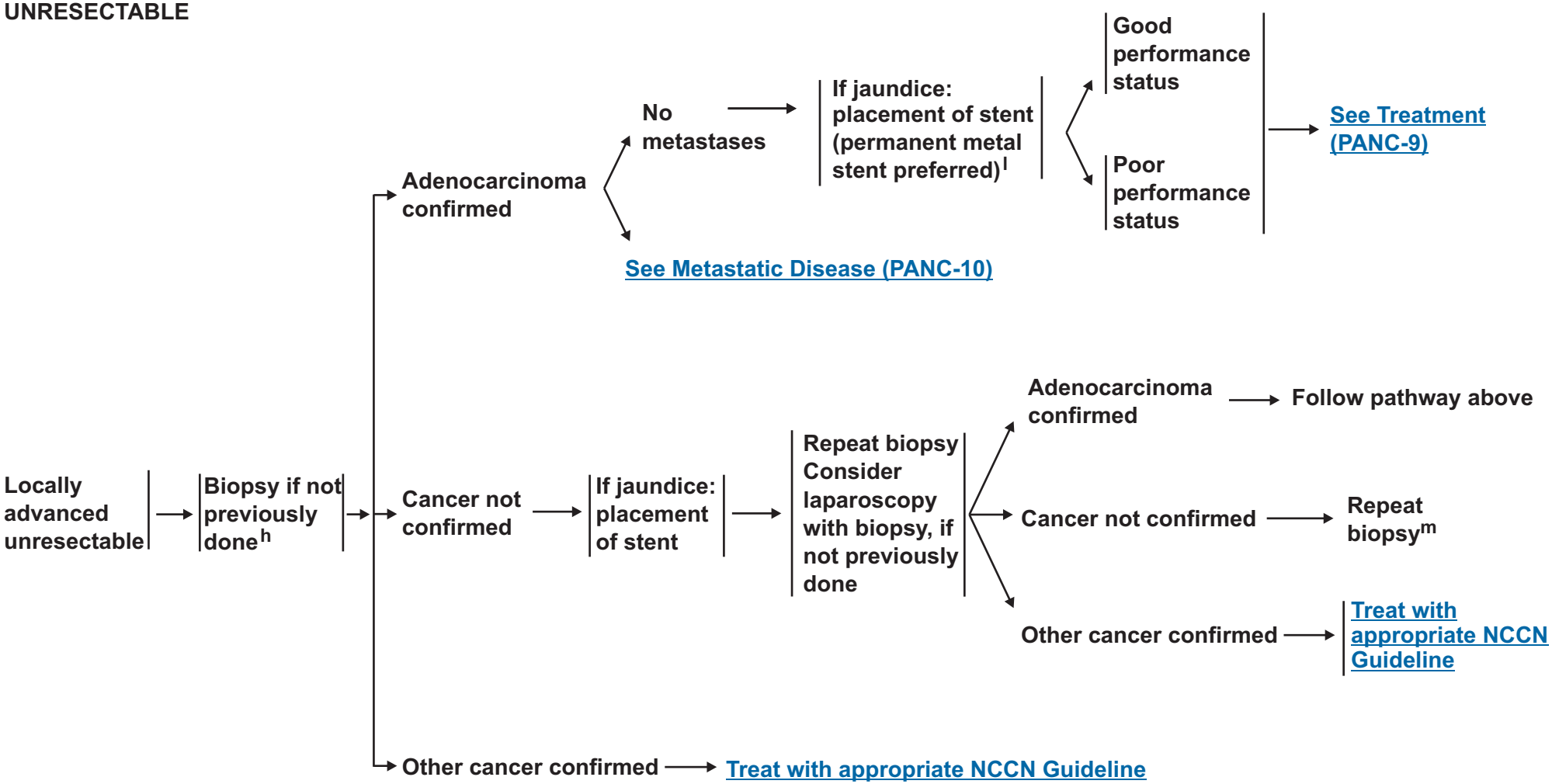
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LOCALLY ADVANCED UNRESECTABLE WORKUP



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

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LOCALLY ADVANCED UNRESECTABLE TREATMENT

Good performance status →
- Clinical trial preferred
  or
- Systemic chemotherapy (gemcitabine based) ± chemoradiation[l,n,o]
  or
- Gemcitabine[p]
  or
- Gemcitabine-based combination therapy[p]

Poor performance status →
- Gemcitabine[p] (category 1)
  or
- Best supportive care[f]

SALVAGE THERAPY

Good performance status →
- Clinical trial (preferred)
  or
- Fluorinated pyrimidine-based therapy[p,q] ± oxaliplatin

→ Best supportive care[f]

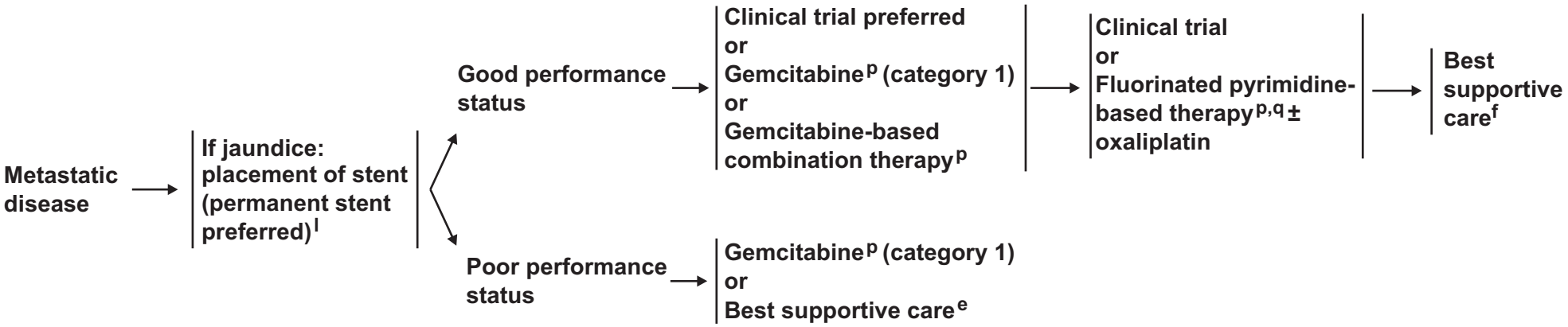
Poor performance status → Best supportive care[f]

[f] See Principles of Palliation and Supportive Care (PANC-C).
[l] See Principles of Radiation Therapy (PANC-D).
[n] Laparoscopy as indicated to evaluate distant disease.
[o] Chemoradiation should be reserved for patients who do not develop metastatic disease while receiving systemic chemotherapy. 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.
[p] See Principles of Chemotherapy (PANC-E).
[q] 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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METASTATIC DISEASE | **TREATMENT** | **SALVAGE THERAPY**



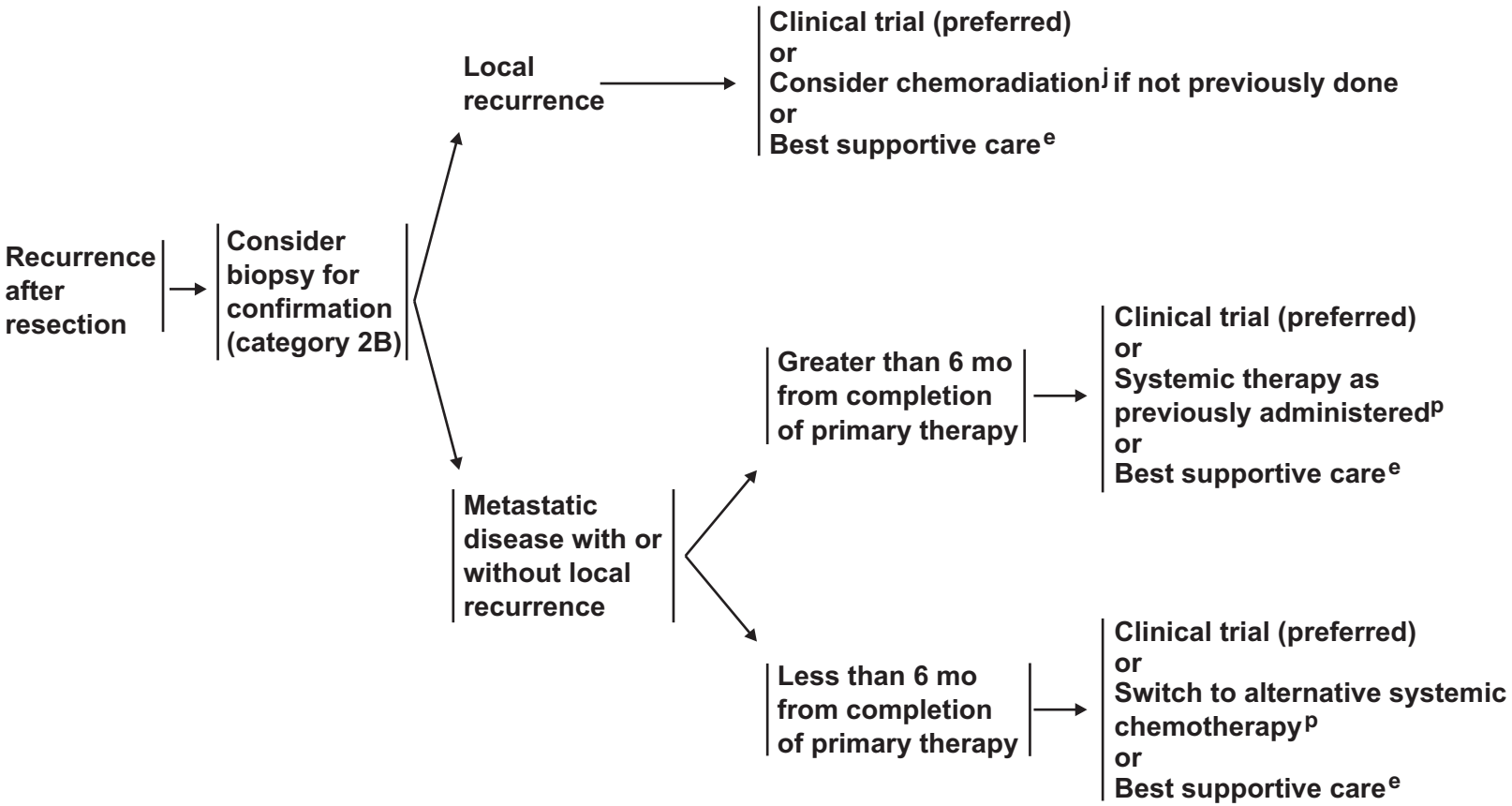
[f] See Principles of Palliation and Supportive Care (PANC-C).
[l] Unless biliary bypass performed at time of laparoscopy or laparotomy.
[p] See Principles of Chemotherapy (PANC-E).
[q] For fluorinated pyrimidine naive patients. Gemcitabine is also an option for patients who received 5-FU chemoradiation and no additional chemotherapy.

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RECURRENCE AFTER RESECTION — TREATMENT — SALVAGE THERAPY



[f] See Principles of Palliation and Supportive Care (PANC-C).
[j] See Principles of Radiation Therapy (PANC-D).
[p] See Principles of Chemotherapy (PANC-E).

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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. Resections should be done at institutions that perform a large number (15-20) of pancreatic resections annually.

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

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

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

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

#6 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, large primary tumors, or large regional lymph nodes).

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

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CRITERIA DEFINING RESECTABILITY STATUS

Tumors considered localized and resectable should demonstrate the following:

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

Tumors considered borderline resectable include the following:

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

NCCN Pancreatic Adenocarcinoma Panel recognize the work of the experts and adapt their criteria to define resectability status. Callery MP, Chang KJ, Fishman EK, et al. Pretreatment Assessment of Resectable and Borderline Resectable Pancreatic Cancer: Expert Consensus Statement. Ann Surg Oncol 2009;16:1727-1733.

Tumors considered to be unresectable demonstrate the following:

- **HEAD**
  - Distant metastases
  - Greater than 180 degrees SMA encasement, any celiac abutment
  - Unreconstructible SMV/portal occlusion
  - Aortic invasion or encasement
- **BODY**
  - Distant metastases
  - SMA or celiac encasement greater than 180 degrees
  - Unreconstructible SMV/portal occlusion
  - Aortic invasion
- **TAIL**
  - Distant metastases
  - SMA or celiac encasement greater than 180 degrees
- **Nodal status**
  - Metastases to lymph nodes beyond the field of resection should be considered unresectable.

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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[1]**
  - **Poor performance status**
    - **Enteral stent[1]**
    - **PEG tube**

- **Severe tumor-associated abdominal pain**
  - **EUS-guided celiac plexus neurolysis (fluoroscopic- or CT-guided if unavailable)**
  - **Consider palliative chemoradiation if not already given as part of primary therapy regimen**

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

- **Pancreatic insufficiency**
  - **Pancreatic enzyme replacement**

- **Thrombembolic disease**
  - **Low molecular weight heparin preferred over warfarin**

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

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

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PRINCIPLES OF RADIATION THERAPY

Increasingly, IMRT is being applied for therapy of pancreatic adenocarcinoma. There is no clear consensus on appropriate maximum dose of radiation in either the adjuvant setting or in the setting of locally advanced disease.

NEOADJUVANT/ADJUVANT RT

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

- **Use of CT simulation and 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]Kalser, Mlt, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch. Surg. 1985;20:899-903.
[3]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.
[4]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 (1 of 2)

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

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

Metastatic

- **Gemcitabine at 1000 mg/m^2 over 30 minutes, weekly for 3 weeks every 28 days, is considered standard front-line therapy for patients with metastatic disease (category 1).**
- **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**
  - **Fixed dose rate gemcitabine + oxaliplatin[2]**
  - **Gemcitabine + fluoropyrimidine[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 5-FU/leucovorin[5] or CapeOx[6]. Results of the CONKO 003 trial demonstrated a significant improvement in overall survival with addition of oxaliplatin to 5-FU /leucovorin.**

Locally Advanced

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

Adjuvant

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

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PRINCIPLES OF CHEMOTHERAPY (2 of 2)

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

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

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

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

[5] Pelzer U, Kubica K, et al. A randomized trial in patients with gemcitiabine refractory pancreatic cancer. Final results of the CONKO 003 study. J Clin Oncol 26: 2008 (May 20 suppl) Abstract 4508.

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

[7] Neuhaus P, Riess H, et al. CONKO-001 Final results of the randomized, prospective, multicenter phase lll trial of adjuvant chemotherapy with gemcitabine versus observation in patients with resected pancreatic cancer. J Clin Oncol26: 2008. (May 20 suppl) Abstract LBA 4504.

[8] Neoptolemos J, Buchler M, Stocken DD, et al. ESPAC-3 (2): A multicenter, international, open-label, randomized, controlled phase III trial of adjuvant 5-fluorouracil/folinic acid versus gemcitabine in patients with resected pancreatic ductal adenocarcinoma [abstract]. J Clin Oncol. 2009;27: 18s (suppl; LBA4505).

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

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Staging

Table 1

American Joint Committee on Cancer (AJCC)
TNM Staging of Pancreatic Cancer (2010)

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)

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

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STAGING CONTINUED ON ST-2

Table 1 continued

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Histopathologic Type

The staging system applies to all exocrine carcinomas that arise in the pancreas. Neuroendocrine tumors have a distinctly different tumor biology and better long-term survival; however, the TNM system provides reasonable stage discrimination. 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)
- Composite carcinoid (combined with adenocarcinoma)
- Adenocarcinoid tumor
- Mixed islet cell and exocrine adenocarcinoma
- Islet cell carcinoma
- Insulinoma
- Glucagonoma
- Gastrinoma
- Vipoma
- Somatostatinoma
- Enteroglucagonoma
- Carcinoid tumor, NOS
- Atypical carcinoid tumor
- Neuroendocrine carcinoma, NOS

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Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Overview

During the year 2010, an estimated 36,800 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 and women.[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. The Panel unanimously endorses participation in a clinical trial over standard or accepted therapy.

Risk Factors and Genetic Predisposition

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

The relationship among diabetes mellitus, alcohol intake, and chronic pancreatitis with adenocarcinoma of the pancreas has been a topic of considerable debate. Numerous studies have shown an association between new-onset diabetes and the development of pancreatic cancer.[11-13] However, certain risk factors such as obesity, and the use of diabetic medications, can impact insulin resistance and blood glucose levels, thereby confounding these analyses.[14,15] Chronic pancreatitis has also been identified as a risk factor for pancreatic cancer.[16,17] Nevertheless, further epidemiologic studies involving careful evaluation of these possible risk factors with adjustments for potential confounders are needed to clarify their impact on pancreatic cancer risk.

True familial pancreatic cancer is rare; however, a genetic predisposition may be present in up to 5%- 10% of patients,[18,19] and familial excess of pancreatic cancer is associated with high risk.[4,19] For example, a germline mutation of the *CDKN2A* (p16) gene has been

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reported in families with pancreatic cancer and melanoma.[20,21] An excess of pancreatic cancer is also seen in families harboring *BRCA2* (breast cancer susceptibility gene-2) mutations,[22,23] and particular mutations in the *PALB2* gene have recently been identified as possibly increasing pancreatic cancer susceptibility.[24] Asymptomatic individuals at high risk for pancreatic cancer (ie, have first-degree relatives with cancer) were assessed using endoscopic ultrasound (EUS) in the Cancer of the Pancreas Screening 2 (CAPS2) project. Preinvasive pancreatic neoplasms were detected suggesting that EUS may have a promising role in screening high-risk patients.[25] The diagnostic yield of pancreatic cancer screening with EUS or MRI in asymptomatic individuals at high risk of familial disease has also been investigated in 2 more recent studies, although the malignant potential of some preinvasive pancreatic lesions and the impact of screening on survival are presently unclear.[26,27]

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.[28,29] Thus, pancreatic carcinoma should be considered in diabetic patients with unusual manifestations, such as abdominal symptoms and continuous weight loss. 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 (see PANC-1; PANC-A).[30,31]

Imaging Evaluations

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

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

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

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In cases where CT is not possible or relatively contraindicated (eg, contrast allergy), magnetic resonance imaging (MRI) with gadolinium infusion can be used to diagnose and stage pancreatic cancer, [39,40] although MRI has not been shown to perform better than CT in this setting. MRI can be a helpful adjunct to CT in the staging of pancreatic cancer, particularly for detecting the presence of extra-pancreatic disease in high-risk patients.[41]

NCCN institutions vary in the use of additional staging technologies, such as EUS. 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.[30] Because this procedure is operator dependent, some divergence in use may occur because of differing technical capabilities and available expertise. The utility of PET/CT for upstaging patients with pancreatic cancer has also been evaluated. In one retrospective study, the use of PET/CT following a standard CT protocol showed increased sensitivity for detection of metastatic disease when compared with the standard CT protocol or PET/CT alone.[42] The sensitivity of detecting metastatic disease for PET/CT alone, standard CT alone, and the combination of PET/CT and standard CT were 61%, 57%, and 87%. In this study, the clinical management of 11% of patients with invasive pancreatic cancer was changed as a result of PET/CT findings. Nevertheless, the role of PET/CT in this setting is evolving and has not yet been established. PET/CT is not a substitute for high-quality contrast-enhanced CT, although it can be considered as an adjunct to a formal pancreatic CT protocol in high-risk patients. 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 (see PANC-1).[43]

Patients with a mass in the pancreas on dynamic-phase spiral CT, but no evidence of metastatic disease, should also receive a surgical consultation (see PANC-1). As previously mentioned, EUS may provide useful staging information in pancreatic cancer, particularly through assessment of certain types of vascular invasion.[44,45] EUS can also be used to evaluate periampullary masses, separating invasive from noninvasive lesions. In addition, EUS may have a role in better characterizing cystic pancreatic lesions. On EUS, malignant cystic lesions may present as a hypoechoic cystic/solid mass or as a complex cyst and are frequently associated with a dilated main pancreatic duct. Some therapeutic interventions can also be 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 SMA.[45,46]

Patients without a mass in the pancreas on cross-sectional imaging and without evidence of metastatic disease should undergo additional imaging with EUS and/or endoscopic retrograde cholangiopancreatography (ERCP), as clinically indicated (see PANC-1). It can be difficult to discriminate between benign and malignant strictures or stenosis; however, severe stenosis and marked proximal dilatation more often indicate malignancy.[47] EUS is usually the preferred approach, with ERCP reserved for patients requiring biliary decompression. Stent placement at the time of ERCP can be used to palliate biliary obstruction when surgery is not elected, or if surgery must be delayed. MRI/magnetic resonance cholangiopancreatography (MRCP) is considered to be equivalent to EUS/ERCP in this setting. If studies are consistent with pancreatic cancer, then surgical consultation is recommended.

Restaging with high quality abdominal and chest imaging is also recommended following surgery of resectable disease before initiation of adjuvant therapy (see PANC-7). It should also be performed after administration of each treatment modality when systemic gemcitabine

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is followed by chemoradiation in the adjuvant setting. In addition, such restaging is also recommended following administration of neoadjuvant therapy and prior to surgical resection for patients with borderline resectable disease (see PANC-5; PANC-6)

Laparoscopy

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

Some recent evidence provides support for a selective approach to staging laparoscopy (ie, it is performed if the presence of occult metastatic disease is suggested by high-quality imaging or certain clinical indicators).[50,51] For example, preoperative serum CA 19-9 levels > 100 U/mL have been associated with a greater likelihood of advanced disease and an increased probability of a positive finding on staging laparoscopy.[52] In a recent prospective review of 838 patients who were diagnosed with resectable pancreatic tumors on imaging evaluation during the period between 1995 and 2005, 8% were found to have unresectable disease (12% yield if only pancreatic adenocarcinoma was considered) following subsequent laparoscopy performed at a single institution.[53] Characteristics associated with an increased laparoscopic yield include the location of the tumor, tumor histology, the presence of weight loss and jaundice, and the facility conducting the imaging evaluation.

Diagnostic staging laparoscopy to rule out subradiologic metastases (especially for body and tail lesions) is used routinely in some NCCN institutions prior to surgery or chemoradiation, or selectively in patients who are at higher risk for disseminated disease (eg, borderline resectable disease; markedly elevated CA 19-9; large primary tumors).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 2A recommendation for patients staged with resectable pancreatic cancer considered to be at increased risk of disseminated disease (see PANC-3; PANC-A), and as a category 2B recommendation for patients with borderline resectable disease prior to and following administration of neoadjuvant therapy since it is not uniformly done at all NCCN institutions (see PANC-5; PANC-6; PANC-4). The Panel considers positive cytology from washings obtained at laparoscopy or laparotomy to be equivalent to M1 disease.[54]

Tumor-Associated Antigens

Many tumor-associated antigens have been studied in connection with pancreatic adenocarcinoma, including carcinoembryonic antigen (CEA), pancreatic anti-oncofetal antigen, tissue polypeptide antigen, cancer 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 (see below),[55] and CA 19-9 may be falsely positive in cases of benign biliary obstruction[56] or undetectable in Lewis-negative individuals.[57] Preoperative measurement of CA19-9 levels should be performed after biliary decompression is complete (see PANC-2).

A low postoperative serum CA 19-9 level, and a decrease in serial CA 19-9 levels following surgery, have been found to correlate with survival

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for patients undergoing resection for pancreatic cancer.[58,59,60] In one prospective study of patients undergoing surgery with curative intent, median survival for the group of patients with post-resectional CA 19-9 levels of < 180 U/mL was significantly higher compared with the group with higher levels of CA 19-9 following surgery (hazard ratio=3.53; P<0.0001). Similarly, in a prospective study of patients with advanced pancreatic cancer, a dichotomized pretreatment CA 19-9 serum level was shown to be an independent prognostic factor for survival.[61] However, data are conflicting regarding the predictive significance of CA 19-9 response following chemotherapy in patients with advanced disease.[61-65] The Panel recommends measurement of serum CA 19-9 level following surgery prior to administration of adjuvant therapy (see PANC-7). Of note, there is no FDA-approved testing methodology for measuring serum CA 19-9 levels, and a number of different methods are commercially available for quantifying this tumor-associated antigen. Measurements of serum levels of CA 19-9 using one testing method cannot be extrapolated to results obtained using a different procedure.

Differential Diagnoses

Chronic pancreatitis and other benign conditions (eg, autoimmune pancreatitis) are in the differential diagnosis of patients suspected of having pancreatic cancer.[66-70]

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

The finding of increased serum immunoglobulin (Ig) G levels is supportive of a diagnosis of autoimmune pancreatitis, although an elevated serum IgG4 level is the most sensitive and specific laboratory indicator. The classic appearance of the pancreas on abdominal CT in patients with diffuse pancreatic involvement is a sausage-shaped enlargement of the organ with a capsule-like peripheral rim surrounding the pancreas, although focal enlargement of the pancreas is observed in some cases.[71] Cardinal histologic features of autoimmune pancreatitis include prominent lymphocytic infiltration of the pancreatic parenchyma with associated fibrosis.

Pathology

Biopsy

Although a histologic diagnosis is not required before surgery, it is necessary before administration of neoadjuvant therapy (see PANC-4; PANC-5; PANC-6), and for patients staged with locally advanced and unresectable pancreatic cancer or metastatic disease (see PANC-8). 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-4). 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.[74] A negative biopsy should be confirmed by at least one repeat EUS biopsy (see PANC-5; PANC-6) However, in some cases (eg, borderline resectable disease), treatment (ie, laparotomy) may still be recommended for these patients following 2 negative biopsies, especially if there is clinical and radiographic evidence strongly suggestive of pancreatic cancer (see PANC-5; PANC-6).[33] In situations where clinical and imaging findings indicate that locally advanced disease is present, laparoscopy with biopsy can be considered if repeat FNA biopsy is negative (see PANC-8). In patients without obstructive jaundice at initial presentation, EUS-FNA is highly accurate and reliable

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for ruling in malignancy; in patients with obstructive jaundice and biliary stricture, EUS-FNA is less accurate.[30] 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.[75] 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.

Specimen orientation, pathologic analysis and reporting

Pathology synoptic reports (protocols) are useful for reporting results from examinations of surgical specimens; these reports assist pathologists in providing clinically useful and relevant information. The 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.

The American Joint Committee on Cancer (AJCC) has developed staging criteria for adenocarcinoma of the pancreas (see Table 1).[76]

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).[77] Although the TNM staging criteria for pancreatic cancer in the 7th edition of the AJCC Cancer Staging Manual have taken into account the fact that tumors of the pancreas are evaluated preoperatively by CT to determine resectability status, these staging criteria also include information that can be determined only through postsurgical pathologic evaluation of resected tumor.[76] For clinical purposes, most NCCN 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.[76]

There is wide variation in the reported R1 rates of pancreaticoduodenectomy specimens.[78] Clear definitions of microscopic margin involvement and a circumferential resection margin are needed. Although several methods of specimen orientation and pathologic analysis have been described, there is no uniform

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consensus on a standardized protocol for the pathological examination of these specimens.[78-80]

A pathologic evaluation of the surgical specimen involves both the pathologist and the surgeon.[78,80] For example, for an evaluation of resection margin status surgical margins need to be inked appropriately and the surgeon must specify whether or not a complete resection was performed in order for the pathologist to be able to distinguish between an R1 and an R2 resection.[81]

Surgical Management

Criteria for Resection

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

The NCCN Panel 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. Based on their clinical experience with the primary management of pancreatic tumors, an expert consensus group has developed criteria to define tumor resectability so as to improve patient selection for surgery and increase the likelihood of an R0 resection.[33] Using these criteria tumors are classified as: resectable; borderline resectable; or unresectable (eg, locally advanced or metastatic disease) (see PANC-B).

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

The likelihood of attaining negative surgical margins (ie, R0 resection) is a key criterion for consideration when determining whether a patient is a potential candidate for resection.[90,91] In this context, a borderline resectable lesion can be defined as one in which there is a higher likelihood of an incomplete (R1 or R2) resection (see PANC-B).

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Primary Surgery for Pancreatic Cancer

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

Because tumors of the body and tail cause symptoms late in their development, they are usually advanced at diagnosis and uncommonly resectable. Patients with tumors in the head of the pancreas, who usually present because of jaundice, are treated with pancreaticoduodenectomy. A review of the biomedical literature indicates that there are no universally accepted surgical techniques for performing this procedure. This complex procedure has several controversial issues associated with it that are discussed in more detail in the following sections. Nevertheless, surgery should be performed only by surgeons capable of managing tumor-vessel involvement.

Preoperative Biliary Drainage

The main goals of preoperative biliary drainage are to alleviate the symptoms of pruritus and cholangitis 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.[92-94] 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.[95-101] In 1999, a retrospective study from Memorial Sloan-Kettering Cancer Center examined 240 consecutive pancreaticoduodenectomies where 53% of patients underwent preoperative biliary decompression.[102] This study found a statistical relationship between the use of preoperative drainage (irrespective of the method used) and increased postoperative complications, including death, in patients who went straight to surgery.

In contrast, the University of Texas MD Anderson Cancer Center reported on their experience with more than 300 patients of whom 57% had preoperative biliary drainage[103] 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. In addition, a recent multicenter, randomized trial comparing preoperative biliary drainage with surgery alone for 202 patients with cancer of the pancreatic head characterized by obstructive jaundice showed the a nearly 2-fold increase in the rate of serious complications in the former group (74% vs. 39%; relative risk in the early-surgery group, 0.54; 95% CI, 0.41-0.71; P<0.001), although no significant differences in surgery-related complications, length of hospital stay, or mortality were observed.[104] Based on these reports, most groups who perform resection first advocate selective use of decompression only in patients who are symptomatic or septic, or in whom surgical resection is significantly delayed. For patients with jaundice undergoing neoadjuvant induction therapy before pancreatic resection, biliary decompression is necessary to initiate therapy and 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) along with antibiotic coverage if symptoms of cholangitis or fever are present (see PANC-2). Endoscopic placement of a temporary stent and normalization of bilirubin levels 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). Placement of a 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).

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Pylorus Preservation

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

Pancreatic Anastomosis

Efforts in this area have focused on preventing pancreatic leaks and fistulas, which are morbid and 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.[113] Furthermore, surgeons have examined various other options for the pancreaticojejunal anastomosis; end-to-end, end-to-side, duct-to-mucosa, and invaginating techniques have all proven to be safe and effective.[114,115] Results of a prospective trial show that pancreatic fistula can be almost entirely avoided by a technique that combines placement/tying of sutures under magnification with meticulous attention to blood supply.[116] Stents used in the 1930s and 1940s continue to be used today, but no data suggest that they decrease leak rates.[117] Pancreatic fistula rates are similar (ranging in most studies from 6% to 16%).[106,114,118] although the exact way to define a pancreatic leak in terms of volume and duration of drainage remains controversial.[119]

In addition to technical modifications, octreotide has been examined for its ability to decrease postoperative pancreaticojejunal leaks in patients undergoing pancreatic resections. However, octreotide did not decrease fistula rates when assessed in two prospective, randomized, double-blind, placebo-controlled studies (ie, University of Texas M. D. Anderson Cancer Center, Johns Hopkins Hospital).[120,121] Finally, the use of fibrin glue sealant does not appear to decrease the rate of pancreatic fistulas.[122]

Portal Vein Resection

Vascular invasion has been a conventional contraindication to pancreatic resection. Early attempts at resection and reconstruction of the SMA and SMV in the 1970s were associated with poor results in a few patients who underwent “regional” pancreatectomy.[123] Both autologous and synthetic grafts were used for arterial and venous reconstructions. As morbidity from pancreaticoduodenectomy decreased, a subset of patients was identified who were in need of resection of the SMV wall to achieve negative margins during removal of their tumors. Thus, 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.[124] Furthermore, long-term outcome is not significantly worse.[125] Although compelling, this approach has not been universally accepted. During

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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.[126-129] A recent study found that properly selected patients (n = 141) with adenocarcinoma of the pancreatic head who required vein resection had a median survival of approximately 2 years, which did not differ from those having standard pancreaticoduodenectomy and was superior to historical patients believed to have locally advanced disease who did not receive surgical treatment.[130] Thus, a few groups have recommended caution and only use vein resection for selected patients.

Extended Lymphadenectomy

The role of lymph node dissection as a component of pancreaticoduodenectomy has remained controversial during the 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[131,132] 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.[133]

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.[134,135] 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.[136,137]

Two prospective, randomized trials have tried to address the role of lymphadenectomy in patients undergoing pancreaticoduodenectomy. The Italian Multicenter Lymphadenectomy Group reported on a series of 81 patients randomly assigned to pancreaticoduodenectomy with or without 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.[138] A larger randomized prospective trial is currently being done at Johns Hopkins Hospital to evaluate the role of extended lymph node dissections.[139] 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.[140]

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

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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[141] 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.[142] 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.[143-147] Interestingly, this effect was also seen in reports from Canada and the Netherlands.[148,149]

The definitions of high and low volume varied among all these studies. However, a striking difference is seen when the mortality rates from pancreaticoduodenectomy in very-low-volume (0-1 procedure/year) and in low-volume (1-2 procedures/year) hospitals are compared with rates in higher-volume hospitals (> 5 procedures/year).[150] In-hospital mortality rates at these very-low-volume and low-volume hospitals were significantly higher than at high-volume hospitals (16% and 12%, respectively, 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.[151] In this study, 6 or more pancreatic resections were performed at only 6.3% of hospitals. The largest difference in operative mortality between very-low-volume (17.6%) and high-volume (3.8%) centers is seen for pancreaticoduodenectomy, 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.

The NCCN Panel recommendation is that pancreatic resections should be done at institutions that perform a large number (>15-20) of pancreatic resections annually (see PANC-A).

A 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.[152] 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<0.001; use of multimodality therapy increased from 26.8% to 38.7%, P<0.001). 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 (38.2%) of these patients with potentially resectable disease were not treated surgically.[153] Nevertheless, the consensus of the Panel is that patients should be selected for surgery on the basis of

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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 Therapy

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.[154] 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 (40891) in patients with both ampullary and pancreatic adenocarcinoma 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.[155] At a median follow-up of 11.7 years, no statistically significant differences were observed in the 2 study arms with respect to progression-free survival or overall survival for the subset of patients with pancreatic cancer.[156]

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

In 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, an ITT analysis of the data showed that the primary endpoint of increased disease-free survival was met (median DFS 13.4 months vs. 6.9 months; P<0.001, log rank).[160] Recently, final results from this study showed median overall survival to be improved significantly for patients in the gemcitabine arm (22.8 months vs. 20.2 months; P=0.005).[161] Significant differences in median overall survival only became apparent at 2 years with an absolute survival difference of 12.0% observed between the 2 groups at 5 years (21% vs. 5%).

The Radiation Therapy Oncology Group (RTOG) is a phase III study (RTOG 97-04) which evaluated pre- (3 weeks duration) and post-chemoradiation 5-FU (3 months duration) versus pre- and post-chemoradiation gemcitabine for postoperative adjuvant treatment of resected pancreatic adenocarcinoma.[162] This trial which utilized daily fractionated radiotherapy included prospective quality assurance of all patients, including central review of preoperative CT imaging and radiation fields.[163] Results of this study showed that, for patients with tumors of the pancreas head (representing 388 of the 451 patients enrolled in the trial), there was a non-statistically significant increase in overall survival in the gemcitabine arm compared with the 5-FU arm (median and 3-year survival of 20.5 months and 31% vs. 16.9 months and 22%; P=0.09); this benefit became more pronounced on multivariate analysis. Whereas results from the RTOG trial suggest a possible advantage for adjuvant therapy with gemcitabine over

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

Results of RTOG 97-04 cannot be directly compared with the results of the CONKO-001, ESPAC-1, or ESPAC-3 trials because of differences in treatment design 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). In addition, limitations of some of these trials include problems with surgery and pathology quality control, and inconsistencies in postoperative restaging with CT.[165] However, it is interesting to note that median overall survival for patients in the gemcitabine arm of CONKO-001 (22.8 months), the gemcitabine-containing arm of RTOG 9704 (20.5 months), the bolus 5-FU/leucovorin arm of ESPAC-1 (20.1 months) and the gemcitabine and 5-FU/leucovorin arms of the ESPAC-3 study (23.6 and 23.0 months) are 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/leucovorin or capecitabine are listed in the guidelines as options for adjuvant treatment. All of these adjuvant therapy options are designated as category 2A recommendations, with the exception of capecitabine (category 2B). However, it was the consensus of the Panel that when chemotherapy alone is the choice of adjuvant therapy, gemcitabine is preferred over either 5-FU/leucovorin or capecitabine for most patients due to its more favorable toxicity profile, and that systemic gemcitabine should be administered prior to 5-FU-based chemoradiation when chemoradiation is the adjuvant therapy choice.

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-D).[166] 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 following systemic gemcitabine in the adjuvant setting (see PANC-7) since 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.[167-169] Therefore, the Panel recommends that when chemoradiation is considered as adjuvant therapy, it should be administered following an adequate course (ie, up to 4 months) of systemic chemotherapy.

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-7). It is recommended that the patient undergo a pretreatment baseline assessment, including CT scan and CA 19-9 level, following surgery to evaluate for the presence of metastatic disease before adjuvant chemoradiation is initiated. Further, the Panel recommends restaging a patient with a CT scan following systemic chemotherapy, if it will precede chemoradiation (see PANC-7). Adjuvant therapy is not restricted to patients who have not had neoadjuvant therapy but adjuvant chemoradiation cannot be administered to patients who have received neoadjuvant chemoradiation.

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Preoperative (Neoadjuvant) Therapy

Novel contemporary approaches to adjuvant therapy have focused on preoperative (neoadjuvant) therapy with the goal of improving overall survival.[170,171] Although not widely investigated, a number of studies have evaluated the use of neoadjuvant chemoradiation in patients with resectable disease.[37,38,172-174] To date, however, no randomized trials have addressed this issue. A retrospective review of the collective experience at MD 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.[173] 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.[90,170,175] In an analysis of 132 consecutive patients, the MD 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.[173]

Some studies have addressed the use of preoperative chemoradiation therapy to convert selected patients with unresectable disease to a resectable status.[171,172,175-180] Although emerging evidence suggests that there is a better chance of margin-negative resection with preoperative therapy,[181] 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.

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

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

The majority of NCCN centers prefer an initial approach involving neoadjuvant therapy, as opposed to immediate surgery, for patients with borderline resectable disease, and the Panel recommends

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neoadjuvant therapy as an option to upfront resection following clinical staging of disease as borderline resectable (see PANC-4). Since most but not all NCCN centers administer neoadjuvant therapy to patients with borderline resectable disease, both of these options are designated as category 2B recommendations. EUS-directed biopsy is the preferred method of obtaining histological confirmation of disease in these patients, and such confirmation is necessary before administering neoadjuvant therapy. A repeat biopsy should be performed in cases where the initial biopsy results are negative. In addition, staging laparoscopy, performed to evaluate for the possible presence of metastatic disease, is also recommended (category 2B) before and after neoadjuvant therapy (see PANC-4; PANC-5; PANC-6). Placement of a stent is recommended prior to initiation of neoadjuvant therapy in patients with jaundice (PANC-6). Neoadjuvant therapy regimens are often similar to those used to treat locally advanced disease (see section on Chemoradiation for Locally Advanced Disease - below). Abdominal and chest imaging should be repeated following neoadjuvant therapy.

The Panel also recommends that neoadjuvant therapy in the context of a clinical trial be considered for patients clinically staged as having resectable disease (see PANC-3). 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-8; PANC-9; PANC-D), although the utility of chemoradiation in this population of patients is controversial.[185] The role of chemoradiation was initially defined in a trial conducted by GITSG.[186] 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-D).[166,187] 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, systemic chemotherapy following by chemoradiation therapy is a recommended option for patients with unresectable disease, no metastases, and good performance status.

Gemcitabine has also been used as a radiation sensitizer.[183,184,188-190] There is evidence to suggest that concurrent gemcitabine and radiation can yield similar outcomes when compared with 5-FU--based chemoradiation,[190,191] although no randomized trials have directly assessed whether any of these modifications are superior to the original trial results reported by GITSG. Results from a recent phase II study of patients with locally advanced pancreatic adenocarcinoma from the North Central Cancer Treatment Group (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.[192] Chemoradiation is included in the guidelines as an option for patients with locally advanced unresectable disease with no metastases who have a good performance status (category 2A; see PANC-8; PANC-9). The Panel recommends that an adequate course (ie, up to 4 months) of initial systemic chemotherapy (gemcitabine-based) be administered to

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patients with locally advanced disease for whom chemoradiation therapy is planned since emerging data suggest that a period of chemotherapy followed by consolidated chemoradiation may be preferable to upfront chemoradiation.[167-169,193] A treatment approach employing an initial 3-4 month course of chemotherapy may facilitate systemic disease control while simultaneously helping to uncover whether the disease is rapidly progressive. For example, a retrospective analysis of 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.[167] This approach is currently being evaluated in an ongoing phase III trial (GERCOR-LAP-07-D07-1). When systemic chemotherapy precedes administration of chemoradiation, the Panel recommends restaging with a CT scan prior to RT.

Chemotherapy without RT is also an option for patients with locally advanced pancreatic cancer, especially for patients with poor performance status (see PANC-8; PANC-9; PANC-E). Results of 2 early randomized trials comparing chemoradiation to chemotherapy in locally advanced disease were contradictory.[194,195] A phase III randomized trial (ECOG-4201) which assessed gemcitabine compared with gemcitabine plus RT followed by gemcitabine alone in patients with locally advanced, unresectable pancreatic cancer was closed early due to poor accrual. However, an ITT analysis of data for the 74 patients enrolled in this study showed that median overall survival was significantly longer in the chemoradiation therapy arm of the study (11.0 months vs. 9.2 months; P=0.034).[196] The benefit of chemotherapy versus chemoradiation was also addressed in the phase III FFCD-SFRO study from France in which patients with locally advanced pancreatic cancer were randomly assigned to receive either gemcitabine alone or intensive induction regimen of chemoradiation with 5-FU plus cisplatin followed by gemcitabine maintenance treatment.[197] In this study, gemcitabine alone was associated with a significantly increased overall survival rate at 1 year compared with chemoradiation (53% vs. 32%). Although this study was stopped before the planned inclusion, patients in the chemoradiation arm experienced increased toxicity and were more likely to 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.

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 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-C). 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

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instance, patients who complain of intractable nausea and vomiting may have gastric outlet obstruction rather than chemotherapy-induced emesis. Peritoneal carcinomatosis may manifest as ascites or in its more subtle form, as abdominal bloating, decreased oral intake, and constipation.

Role of Gemcitabine

For patients with locally advanced or metastatic disease, gemcitabine has been established as providing clinical benefit and a modest survival advantage over treatment with bolus 5-FU.[198] The 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-10; PANC-E).[198] The NCCN Panel also debated whether gemcitabine monotherapy should be recommended for patients with unresectable, locoregional disease and a poor performance status. Because the approved indications for gemcitabine include 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-8; PANC-9). For patients who derive clinical benefit from initial gemcitabine treatment in the setting of locally advanced disease, without developing distant disease, subsequent chemoradiation may enhance local control. Following disease progression, fluorinated pyrimidine-based therapy is an option for some patients (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.[199] 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.[200] In the phase III randomized ECOG-6201 trial of patients with advanced pancreatic cancer, median survival was increased in the group receiving FDR gemcitabine vs. standard gemcitabine (6.2 months vs. 4.9 months; P=0.04), although this outcome did not satisfy the protocol-specified criteria for superiority.[201] When gemcitabine is considered for the treatment of advanced pancreatic cancer, the 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). FDR gemcitabine is incorporated into some commonly used gemcitabine-based regimens (eg, GEMOX; [gemcitabine, oxaliplatin]; GTX [gemcitabine, docetaxel, and capecitabine]).[202,203]

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. Gemcitabine has been investigated in combination with potentially synergistic agents (such as cisplatin, oxaliplatin, capecitabine, 5-FU, and irinotecan) or in a multidrug combination (eg, cisplatin, epirubicin, gemcitabine, and 5-FU).[201-215]

Data regarding the survival impact of combining gemcitabine with a platinum agent are conflicting, and results of randomized controlled

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trials have not provided support for use of gemcitabine plus cisplatin in the treatment of patients with advanced pancreatic cancer. Three phase III trials evaluating the combination of gemcitabine with cisplatin vs gemcitabine alone in patients with advanced pancreatic cancer failed to show a significant survival benefit for the combination over the single agent.[205,208,214] Similarly, no survival benefit was observed in a phase III trial investigating the addition of oxaliplatin to gemcitabine compared with gemcitabine alone in this patient population, although the combination regimen was superior with respect to response rate, progression-free survival and clinical benefit.[209] Furthermore, the addition of oxaliplatin to FDR gemcitabine in the ECOG-6201 study did not result in a significant improvement in survival over FDR gemcitabine.[201] Nevertheless, selected patients may benefit from this regimen since patients with breast and ovarian cancers who are carriers of a BRCA mutation[216,217] and selected patients with inherited forms of pancreatic cancer [218] may have disease that is particularly sensitive to a platinum agent. A retrospective study from Johns Hopkins of patients with metastatic pancreatic cancer and a family history of breast, ovarian or pancreatic cancers suggested that response to gemcitabine and cisplatin was superior even with one affected relative.[219]

A number of randomized trials have investigated the combination of gemcitabine with a fluoropyrimidine in patients with advanced pancreatic cancer. The ECOG E2297 trial compared gemcitabine monotherapy with gemcitabine and bolus 5-FU/leucovorin in patients with advanced pancreatic cancer; no statistically significant survival advantage was observed for patients receiving the combination regimen.[211] A randomized study in 533 patients with advanced cancer found that progression-free survival and objective response rates were significantly improved in patients receiving gemcitabine plus capecitabine when compared with gemcitabine alone, although a trend toward an improvement in overall survival for the combination arm did not reach statistical significance.[215] Similarly, results from another smaller phase III trial evaluating this combination did not demonstrate an overall survival advantage for overall study population receiving the combination of gemcitabine with capecitabine, although a post-hoc analysis showed overall survival to be significantly increased in the subgroup of patients with good performance status.[206,220] Although there are concerns about dosing and toxicity of capecitabine in a U.S population, results from a recent phase 1/2 study suggest that a biweekly regimen of fixed-dose gemcitabine in combination with capecitabine is both effective and well tolerated in patients with advanced disease.[221] Of note, results from several studies have indicated that the benefit of gemcitabine combination chemotherapy is predominantly seen in patients with good performance status.[206,208,213]

The NCCN Panel considers gemcitabine-based combination therapy with a fluoropyrimidine to be a reasonable option for patients with locally advanced or metastatic disease and a good performance status who are interested in pursuing more aggressive therapy outside a clinical trial (see PANC-10). Further, gemcitabine plus a platinum agent (ie, cisplatin or oxaliplatin) may be a good choice in selected patients with disease characterized by hereditary risk factors (eg, *BRCA* or *PALB2* mutations). However, the Panel does not consider the combination of gemcitabine plus docetaxel[222] or gemcitabine plus irinotecan[210,222,223] to meet criteria for inclusion in the guidelines.

Although phase II trial results of gemcitabine combined with new targeted drugs (eg, bevacizumab, cetuximab) were encouraging,[224,225] results of phase III studies of combinations of gemcitabine with a biologic agent have indicated that only the combination of gemcitabine plus erlotinib is associated with a statistically significant increase in survival when compared to gemcitabine alone.[226-228] Results of the Cancer and Leukemia Group B (CALGB) phase III trial which evaluated gemcitabine and bevacizumab (an anti-VEGF [vascular endothelial

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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.[227] 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.[228] Median survival was 6.24 months and 1-year survival was 23% compared with 5.91 months and 17% in the control arm. Adverse events, such as rash and diarrhea, were increased in the group receiving erlotinib. A recent phase III trial comparing gemcitabine and erlotinib with or without bevacizumab in patients with metastatic pancreatic cancer did not improve overall survival although a significant improvement in progression-free survival was observed with the addition of bevacizumab.[229] Erlotinib in combination with gemcitabine has been approved by the Food and Drug Administration (FDA) 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-8; PANC-9; PANC-10).

Results from the recently presented preplanned interim analysis of the phase 3 Prodige 4 ACCORD 11 trial evaluating the regimen of 5-FU, leucovorin, oxaliplatin, irinotecan (FOLFIRINOX) vs. gemcitabine alone in patients with metastatic pancreatic cancer and good performance status showed dramatic improvements in both median progression-free survival (6.4 months vs. 3.3 months; P<0.0001) and median overall survival (11.1 months vs. 6.8 months; P<0.0001) in favor of the group receiving FOLFIRINOX.[230] However, there are some concerns about the toxicity of the FOLFIRINOX regimen (ie, approximately one-fourth of the patients receiving this regimen experiencing grade 3/4 fatigue, 46% experienced grade 3/4 neutropenia, and the grade 3/4 febrile neutropenia rate was 5.4%). In addition, it is still unclear whether these results can be generalized to the overall population of patients with metastatic pancreatic cancer characterized by good performance status since the percentage of patients with tumors of the pancreatic head enrolled in the trial was lower than typically observed in this population, raising the question of whether fewer patients had biliary stents. Nevertheless, further investigation of this very promising regimen is encouraged, particularly in the adjuvant setting.

There are also emerging data which suggest that gemcitabine plus nab-paclitaxel,[231] and gemcitabine, docetaxel, capecitabine (GTX)[203] are effective and safe for use in the first-line treatment of patients with advanced pancreatic cancer.

Second-Line Therapy

As cross-sectional body imaging has improved, small-volume metastatic disease is being detected in patients with pancreatic cancer who are otherwise maintaining good functional status. Such patients may initially benefit from gemcitabine-based therapy or from investigational therapy. However, these patients, as well as those with unresectable disease without detectable metastases, will ultimately progress, although a subset of them will continue to have sufficiently good performance status to consider second-line therapy. Gemcitabine may offer palliative benefits in the second-line setting if patients have not been previously treated with gemcitabine.[232] For patients who have received prior gemcitabine-based therapy, the NCCN Panel encourages treatment in a clinical trial. However, when investigational

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therapy is not available, treatment options for fluorinated pyrimidine naïve patients include either capecitabine or 5-FU/leucovorin with or without oxaliplatin. (see PANC-8; PANC-9; PANC-10; PANC-E).[233-236] Note that the capecitabine dose (1,000 mg/m^2 PO twice daily) recommended in the algorithms (see PANC-E) 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).[235] Of note, recent results from the phase III CONKO 003 trial showed significant improvements in both median progression-free survival (13 weeks vs. 9 weeks; P=0.012) and median overall survival (20 weeks vs. 13 weeks; P=0.014) when oxaliplatin was added to 5-FU/leucovorin,[233] making this regimen the standard approach for second-line therapy for patients without prior exposure to fluoropyrimidine-based therapy.

Recurrent Disease

For patients experiencing a recurrence of disease following resection (see PANC-11), the Panel recommends consideration of confirmatory biopsy (category 2B). Chemoradiation can be considered if not previously administered in those patients with local disease recurrence only. For patients for whom there is evidence of metastatic disease (with or without a local recurrence), treatment decisions are influenced by the length of time from completion of adjuvant therapy to the detection of metastases. If adjuvant therapy was completed less than 6 months prior to development of metastatic disease, the Panel recommends that an alternative chemotherapy option be administered, although systemic therapy as previously administered is recommended when this period is greater than 6 months. In all cases of recurrent disease, a clinical trial is the preferred option and best supportive care should also be administered (see PANC-C).

Future Clinical Trials: Recommendations For Design

In 2007, a meeting was convened by the National Cancer Institute's Gastrointestinal Cancer Steering Committee in recognition of the failure of a number of recent phase 3 trials to show clinically significant benefit for patients with pancreatic cancer, and to address the importance of integrating basic and clinical knowledge in the design of clinical trials in pancreatic cancer. Meeting participants included representatives from industry, government and the community, as well as academic researchers and patient advocates. Several important themes emerging from this meeting are summarized below and the recommendations put forward by the committee are endorsed by the NCCN Pancreatic Adenocarcinoma Panel.[237]

- With the emergence of new agents to treat pancreatic cancer, particularly biologics, clinical trial strategies incorporating principles of molecular biology and new imaging methods as well as results from preclinical studies are important
- For patients enrolled in clinical trials, banking of tumor tissue samples should be required along with paired blood and serum samples
- Biomarkers which serve as surrogate markers of the anticancer effects of investigational agents should be sought, and assays to measure such biomarkers should be well validated
- Clinical trials should enroll homogeneous patient populations with respect to disease stage (ie, separate trials for patients with locally advanced disease and metastatic disease) and patient performance status; Criteria for selecting study populations should take into account the putative differential

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efficacy of the agent (ie, vaccines in patients with early-stage disease)

- Phase 3 trials should not be initiated in the absence of clinically meaningful efficacy and safety signals in the phase 2 setting.
- Phase 2 and 3 clinical trials should have a primary endpoint of overall survival
- Quality control standards for preoperative imaging interpretation, pathologic assessment of tumor specimens, and surgical selection criteria are critical when evaluating adjuvant therapies

Palliation of Locally Advanced and Metastatic Disease

A significant subset of patients with pancreatic cancer will require substantial palliative interventions that, in many respects, are unique to the disease. For patients with locally advanced unresectable and metastatic disease, the multidisciplinary management of symptoms due to biliary obstruction, gastric outlet obstruction, and cancer-related pain is of primary importance (see Principles of Palliation and Supportive Care [PANC-C]).

Biliary obstruction

Approximately 65%-75% of patients with pancreatic cancer develop symptomatic biliary obstruction.[238] For patients diagnosed with unresectable disease and biliary obstruction on initial evaluation, the best palliation is provided by an endoscopic biliary stent, especially when anticipated survival is limited. In most cases, a permanent stent is recommended unless biliary bypass is performed (see PANC-6; 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.[239] 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.[240]

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.[241] Durable palliation of biliary obstruction can often be achieved with an expandable metallic biliary endoprosthesis (eg, Wallstent, Boston Scientific).[241]

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-C). 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

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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.[238]

Gastric outlet obstruction

Symptomatic gastric outlet obstruction occurs in 10%-25% of patients with pancreatic cancer.[238] Patients found to have locally advanced or metastatic disease on evaluation who develop gastric outlet obstruction may be palliated with an endoscopically placed enteral stent, especially if their life expectancy is limited or their performance status is poor.[241] An alternative for these patients is percutaneous endoscopic gastrostomy (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-C).

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.[242,243] In both studies, approximately 20% of patients who did not undergo a prophylactic gastrojejunostomy developed late gastric outlet obstruction that required therapy. In both studies, prophylactic retrocolic gastrojejunostomy significantly decreased the incidence of late gastric outlet obstruction but did not extend the length of stay or increase complication rates, such as delayed gastric emptying.

If staging laparoscopy 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.[244] 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.[244,245] Minimally invasive techniques include EUS-guided and percutaneous fluoroscopic- or CT-guided celiac plexus neurolysis (see PANC-C), but laparoscopic, thoracoscopic, and open approaches can also be used. If staging laparoscopy reveals unresectable disease, palliation of tumor-associated abdominal pain may be provided by laparoscopic celiac plexus neurolysis, depending on life expectancy and surgical expertise. In selected patients with severe local back pain, radiation therapy may be considered, even in the setting of metastatic disease.

Additional palliative interventions

Pancreatic insufficiency

Exocrine enzyme insufficiency in pancreatic cancer is caused by tumor-induced damage to the pancreatic parenchyma and/or the pancreatic duct, as well as surgical removal of pancreatic tissue.[246,247] Oral pancreatic exocrine enzyme replacement therapy is recommended for

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patients with pancreatic cancer who have symptoms of exocrine enzyme deficiency (eg, steatorrhea) (see PANC-C).

Treatment of thromboembolic disease

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

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-C). 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-7). 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 relatively high likelihood of a poor outcome for 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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