National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Pancreatic Adenocarcinoma

Version 1.2012

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NCCN Guidelines™ Version 1.2012 Panel Members
Pancreatic Adenocarcinoma

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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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NCCN Guidelines™ Version 1.2012 Updates
Pancreatic Adenocarcinoma

Updates in Version 1.2012 of the NCCN Guidelines from Version 2.2011 include:

PANC-1

- Footnote a: Added "interventional endoscopy" to multidisciplinary team. "Multidisciplinary consultation should ideally involve expertise from surgery, diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, and pathology."
- Workup: Added MRI as an option to pancreatic protocol CT.
- Workup: Changed "chest imaging" to "chest CT."
- Workup: Changed "Biopsy confirmation, metastatic site preferred" to "Biopsy confirmation of metastatic site."

PANC-4

- Changed "biopsy negative" to "cancer not confirmed."
- Added "exclude autoimmune pancreatitis" to cancer not confirmed following repeat biopsy.
- Modified footnote h: "There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. 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-7

- Changed "permanent metal stent" to "expandable metal stent."

PANC-8

- Locally advanced, unresectable, good performance status added: gemcitabine + erlotinib (category 1).
- Locally advanced, unresectable, good performance status removed (category 1) following FOLFIRINOX.
- Locally advanced, unresectable, good performance status, salvage therapy added: Chemoradiation if not previously given and if primary site is the sole site of progression.

PANC-9

- For good performance status, added gemcitabine + erlotinib (category 1).

PANC-A

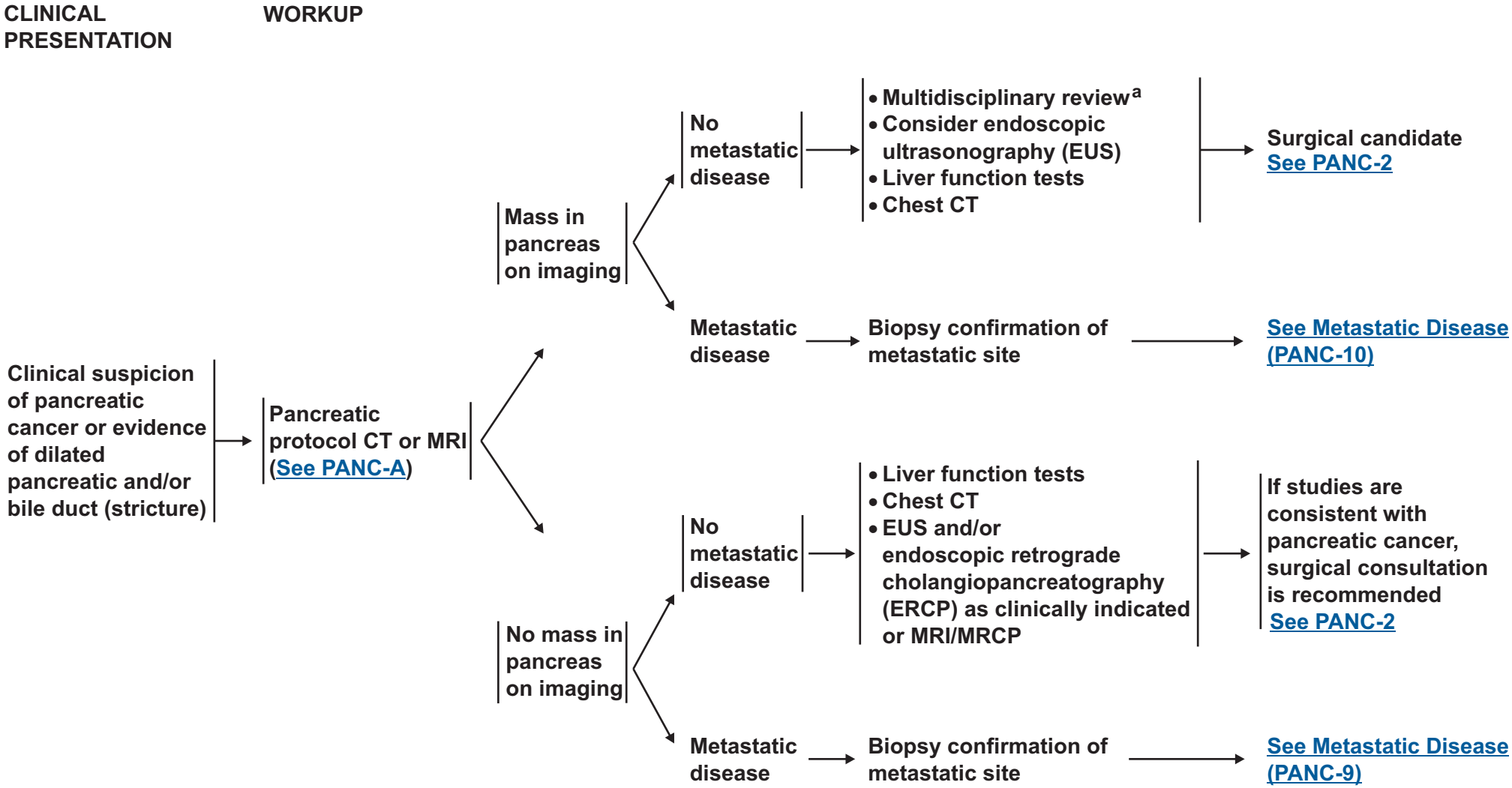
- Changed #1: "radiographic studies" to "imaging studies."
- Added more details to #2: "Imaging should include specialized pancreatic CT or MRI. CT should be performed according to a defined pancreas protocol such as triphasic cross-sectional imaging and thin slices. Optimal multi-phase imaging technique includes a non-contrast phase plus arterial, pancreatic parenchymal and portal venous phases of contrast enhancement with thin cuts (3 mm) through the abdomen. This technique allows precise visualization of the relationship of the primary tumor to the mesenteric vasculature as well as detection of metastatic deposits as small as 3-5 mm. Pancreas protocol MRI is emerging as an alternative to CT for patients."
- Modified #5: "EUS-directed FNA biopsy is preferable to a CT-guided FNA in patients with resectable disease because of better diagnostic yield, safety, and potentially lower risk of peritoneal seeding with EUS FNA when compared with the percutaneous approach."

PANC-E

- Metastatic disease (page 1 of 3)
  - Monotherapy capecitabine was changed from category 2A to a category 2B recommendation (also noted on pages PANC-8 and -9).
  - Combination gemcitabine + cisplatin (especially for patients with possible hereditary cancers) was changed from a category 2B to a category 2A recommendation.
  - Added fluoropyrimidine + oxaliplatin (category 2B) (eg, 5-FU/leucovorin/oxaliplatin or CapeOx)
- Adjuvant therapy (page 2 of 3)
  - Added: "For patients who relapse after receiving adjuvant therapy, subsequent therapy may consist of gemcitabine or gemcitabine-based-combination therapy for patients previously treated with fluoropyrimidine-based therapy, or fluoropyrimidine-based therapy (eg, 5-FU/leucovorin/oxaliplatin[7] or CapeOx)[8] for patients previously treated with gemcitabine-based therapy."

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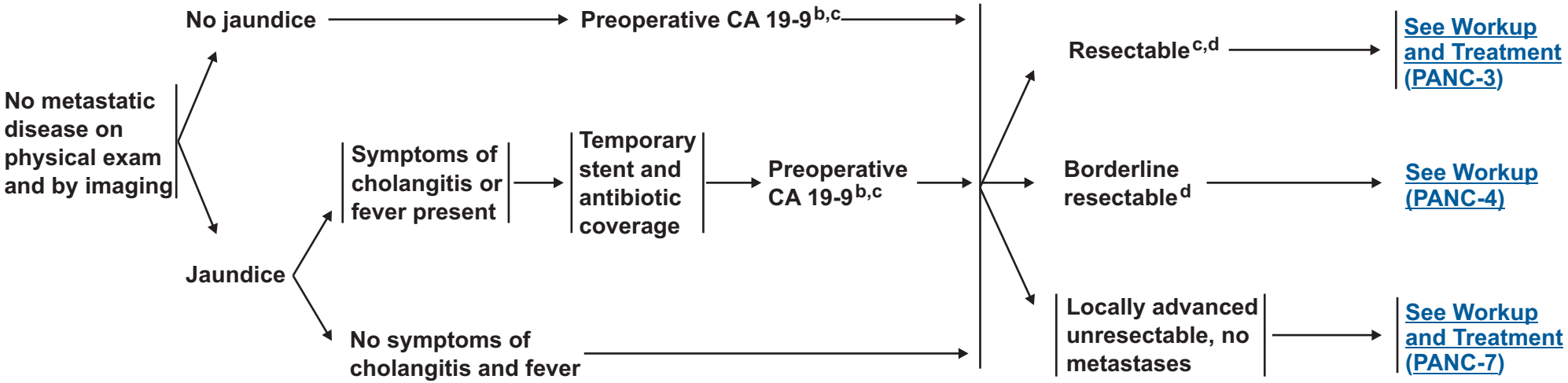
[a]Multidisciplinary review should ideally involve expertise from surgery, diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, surgery, and pathology.

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CLINICAL PRESENTATION

WORKUP



[b] CA 19-9 may be elevated in cases of benign biliary obstruction and does not represent an appropriate baseline until the biliary tree is adequately decompressed and the bilirubin is normal. In addition, CA 19-9 may be undetectable in Lewis antigen-negative individuals.

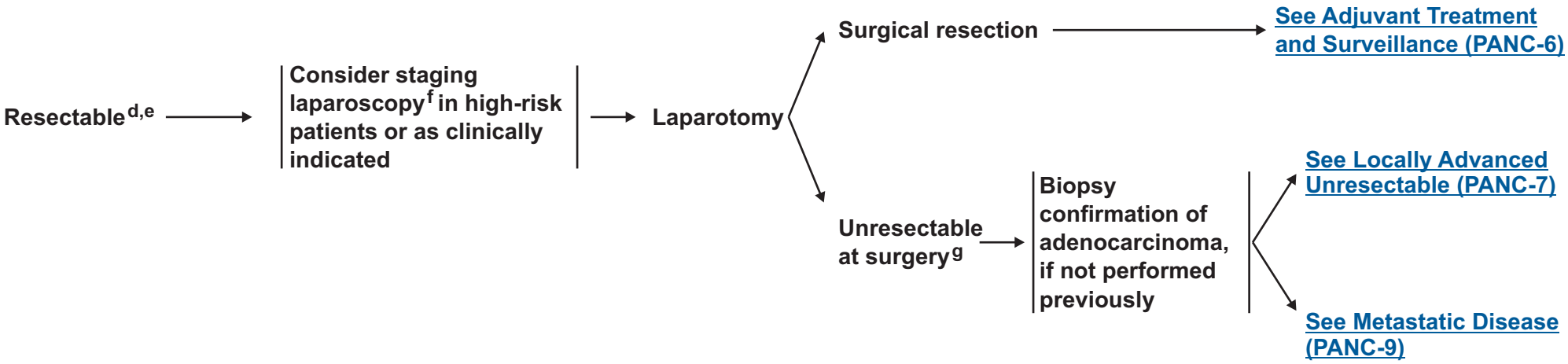
[c] See Principles of Diagnosis and Staging (PANC-A).

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

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RESECTABLE **WORKUP** **TREATMENT**

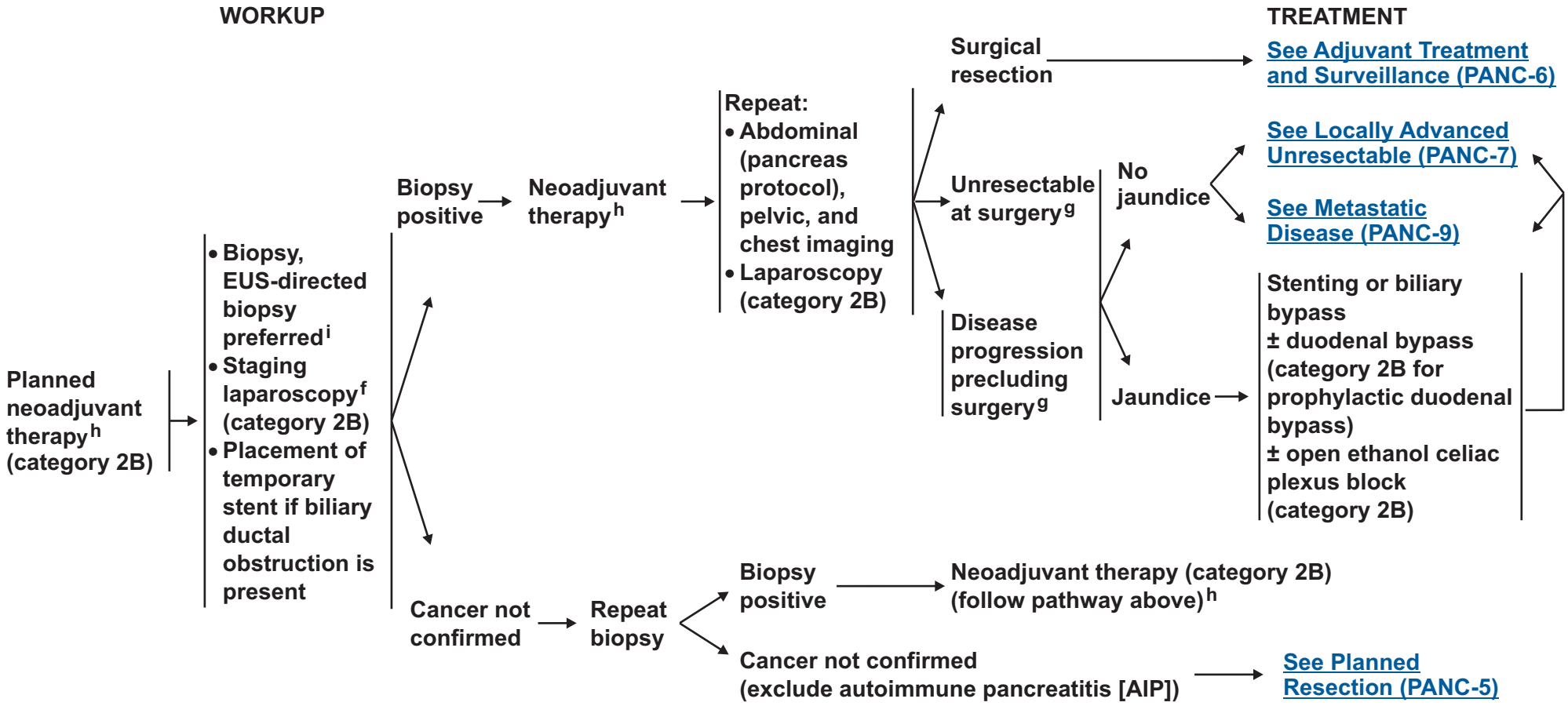


[d] See Criteria Defining Resectability Status (PANC-B).
[e] Consider neoadjuvant therapy on clinical trial, which requires biopsy confirmation of adenocarcinoma. For patients with biliary obstruction, durable biliary decompression is required.
[f] See Principles of Diagnosis and Staging #6 (PANC-A).
[g] See Principles of Palliation and Supportive Care (PANC-C).

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BORDERLINE RESECTABLE[c,d] NO METASTASES, PLANNED NEOADJUVANT THERAPY

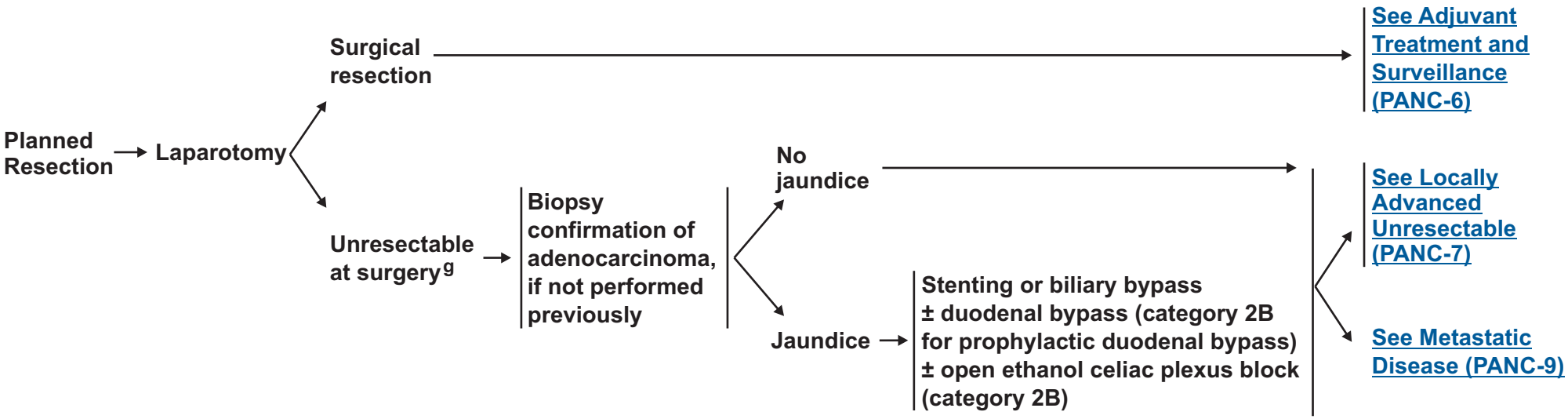


[c] See Principles of Diagnosis and Staging (PANC-A).
[d] See Criteria Defining Resectability Status (PANC-B).
[f] See Principles of Diagnosis and Staging #6 (PANC-A).
[g] See Principles of Palliation and Supportive Care (PANC-C).
[h] There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. 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.
[i] See Principles of Diagnosis and Staging #1 and #5 (PANC-A).

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BORDERLINE RESECTABLE[c,d] NO METASTASES, PLANNED RESECTION



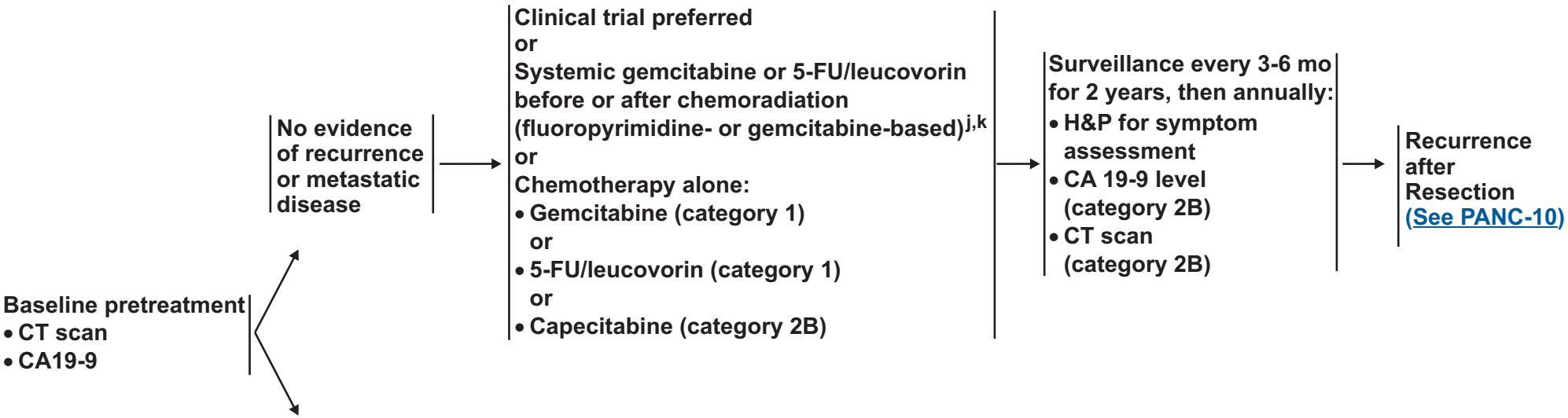
[c] See Principles of Diagnosis and Staging (PANC-A).
[d] See Criteria Defining Resectability Status (PANC-B).
[g] See Principles of Palliation and Supportive Care (PANC-C).

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POST-OPERATIVE ADJUVANT TREATMENT[k]

SURVEILLANCE



See Metastatic Disease (PANC-9)

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

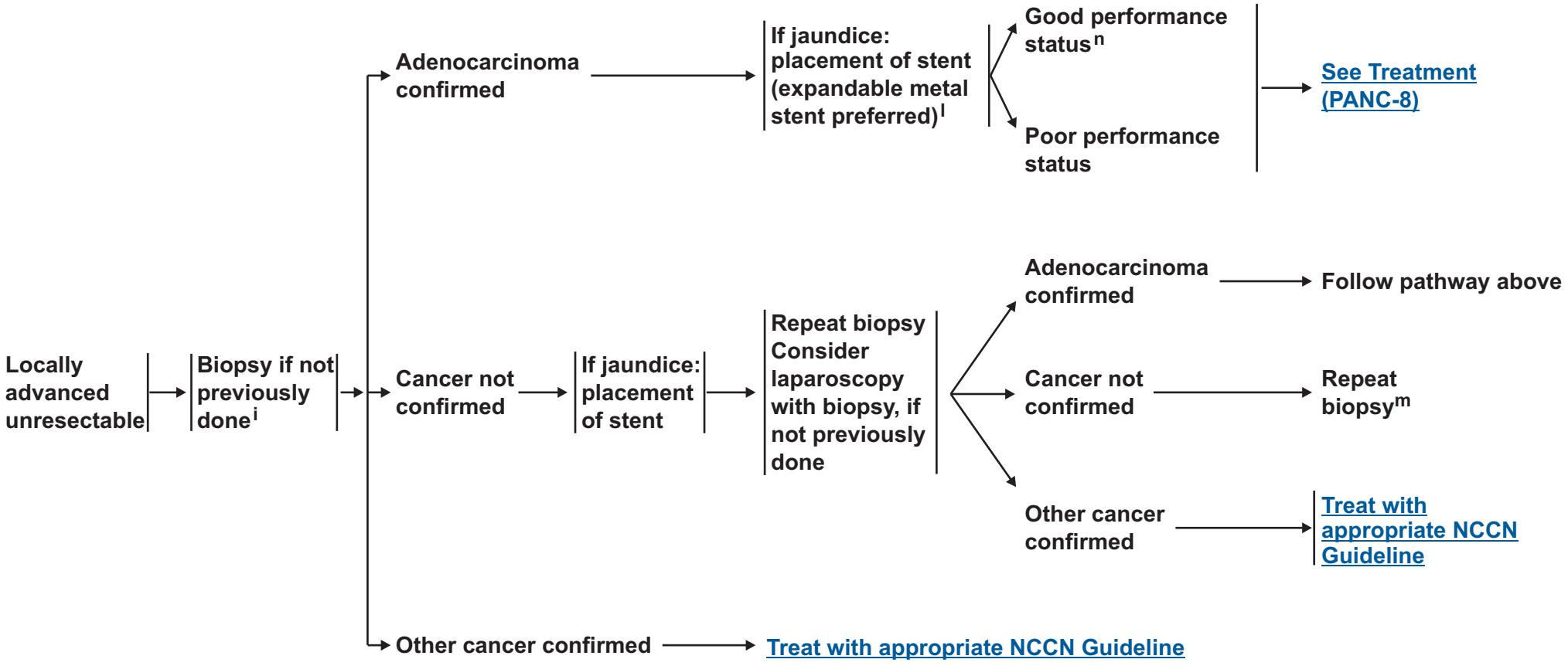
[k] Patients who have received neoadjuvant chemoradiation or chemotherapy are candidates for additional chemotherapy following surgery. Adjuvant treatment should be administered to patients who have not had neoadjuvant chemotherapy and who have adequately recovered from surgery; treatment should be initiated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

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LOCALLY ADVANCED UNRESECTABLE

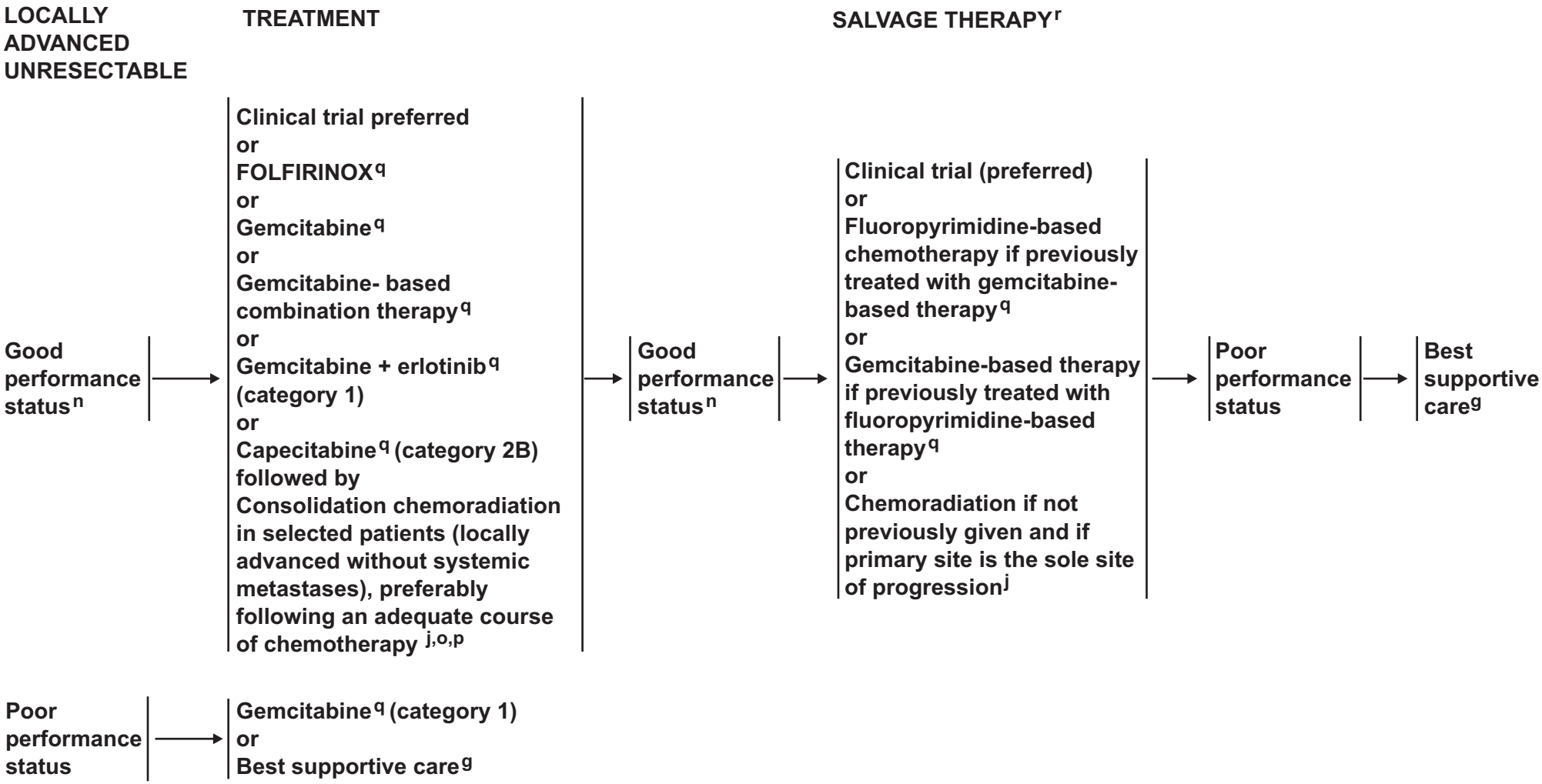
WORKUP



[i] 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.
[n] Defined as ECOG 0,1 with good pain management, patent biliary stent, and adequate nutritional intake.

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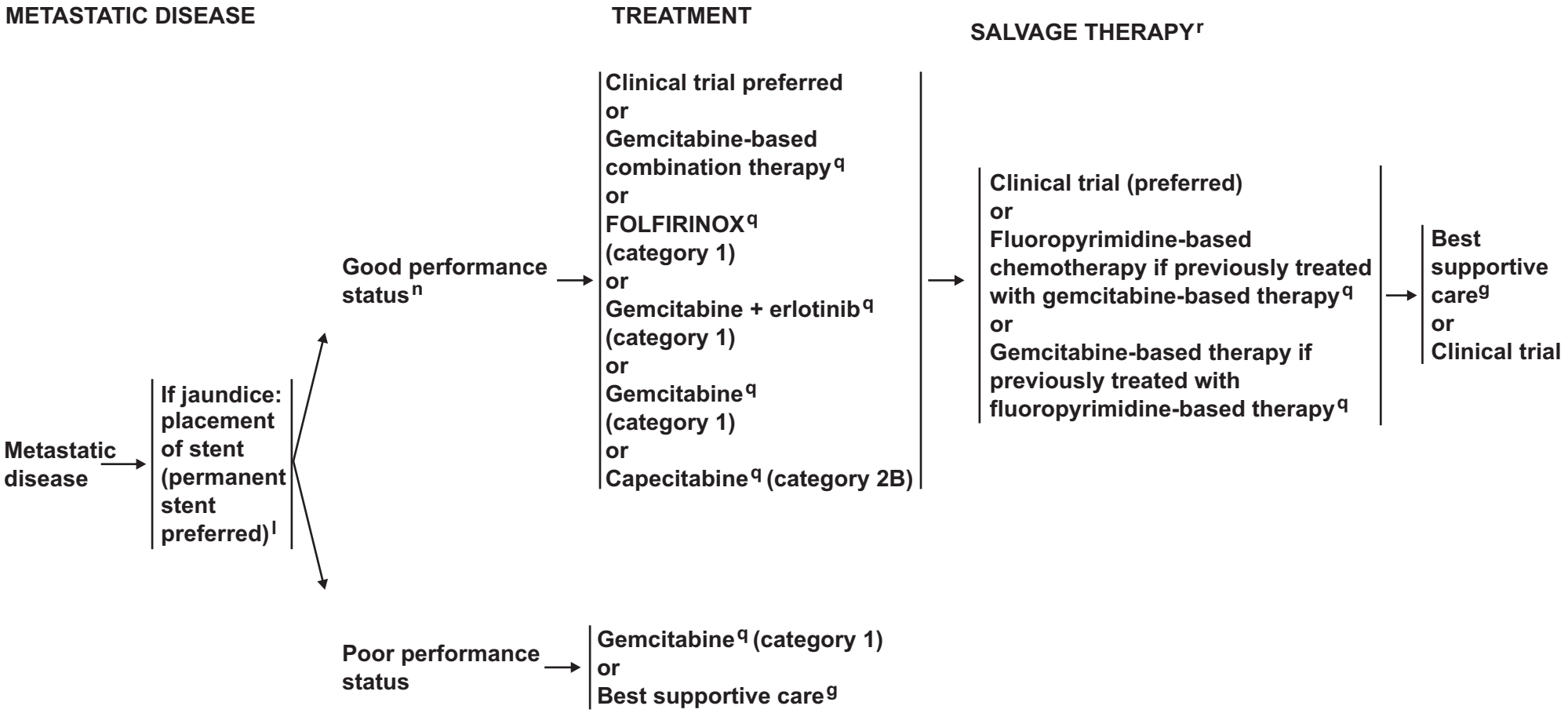
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[g] See Principles of Palliation and Supportive Care (PANC-C).
[j] See Principles of Radiation Therapy (PANC-D).
[n] Defined as ECOG 0-1 with good pain management, patent biliary stent, and adequate nutritional intake.
[o] Laparoscopy as indicated to evaluate distant disease.
[p] 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.
[q] See Principles of Chemotherapy (PANC-E).
[r] Best reserved for patients who maintain a good performance status.

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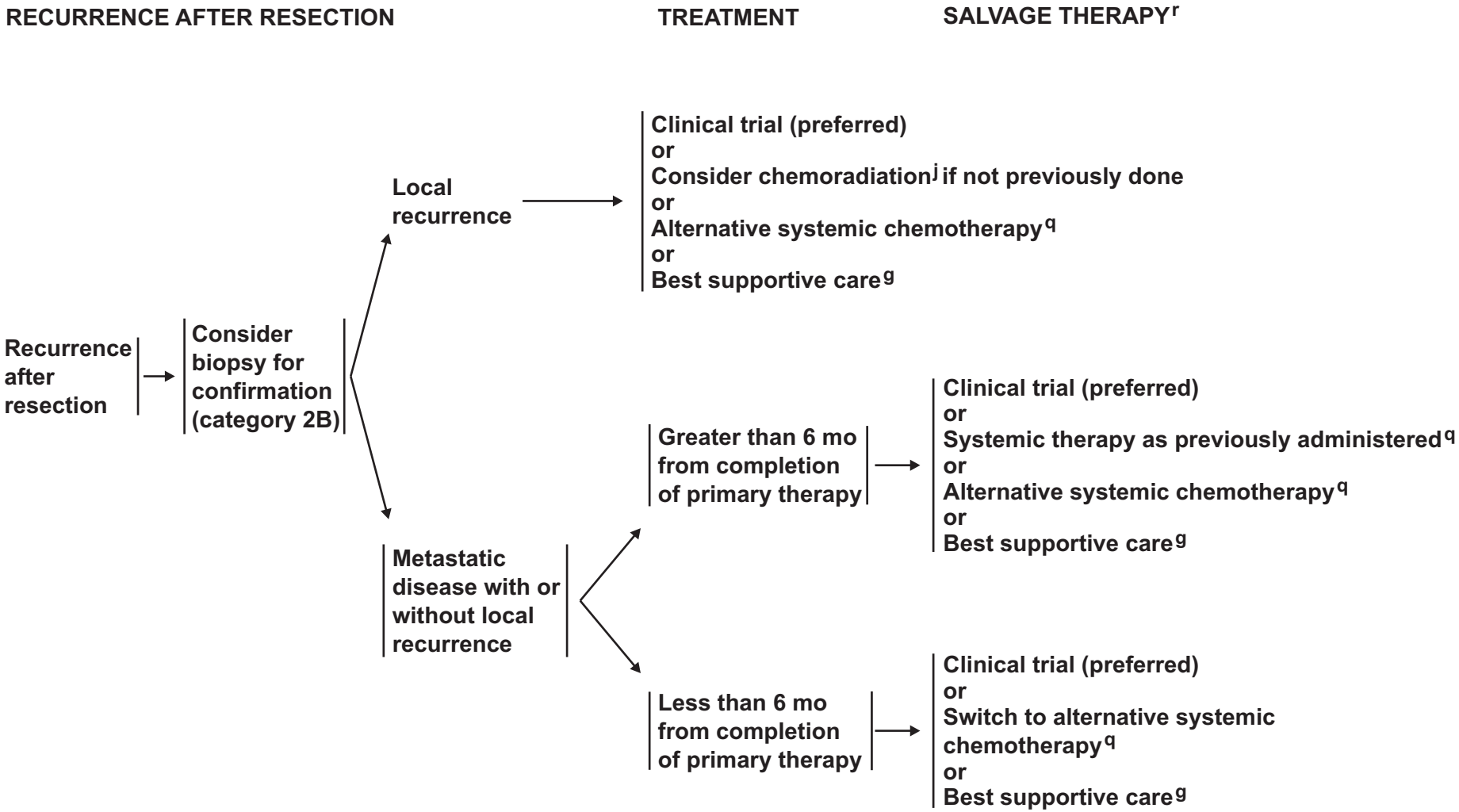
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[g] See Principles of Palliation and Supportive Care (PANC-C).
[l] Unless biliary bypass performed at time of laparoscopy or laparotomy.
[n] Defined as ECOG 0-1 with good pain management, patent biliary stent, and adequate nutritional intake.
[q] See Principles of Chemotherapy (PANC-E).
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[g] See Principles of Palliation and Supportive Care (PANC-C).
[j] See Principles of Radiation Therapy (PANC-D).
[q] See Principles of Chemotherapy (PANC-E).
[r] Best reserved for patients who maintain a good performance status.

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PRINCIPLES OF DIAGNOSIS AND STAGING

#1 Decisions about diagnostic management and resectability should involve multidisciplinary consultation with reference to appropriate imaging 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 or MRI. CT should be performed according to a defined pancreas protocol such as triphasic cross-sectional imaging and thin slices. Optimal multi-phase imaging technique includes a non-contrast phase plus arterial, pancreatic parenchymal and portal venous phases of contrast enhancement with thin cuts (3mm) through the abdomen. This technique allows precise visualization of the relationship of the primary tumor to the mesenteric vasculature as well as detection of metastatic deposits as small as 3-5 mm. Pancreas protocol MRI is emerging as an alternative to CT for patients.

#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 better diagnostic yield, safety, and potentially 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 non-diagnostic 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 CA 19-9, large primary tumors, or large regional lymph nodes).

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

Adapted from: 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[2]

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]**
    - **Percutaneous endoscopic gastrostomy (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, and malnutrition**
  - **Formal Palliative Medicine Service evaluation when appropriate (See NCCN Supportive Care Guidelines)**

- **Pancreatic insufficiency (inadequate production of digestive enzymes)**
  - **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.
[2]Palliative surgical procedures are best reserved for patients with a longer life expectancy.

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PRINCIPLES OF RADIATION THERAPY

General Principles:

- **Patients with pancreatic cancer are best managed by a multi-disciplinary team.[1]**
- **Recommendations for radiation therapy (RT) for such patients are typically made based upon five typical clinical scenarios: 1) neoadjuvant/resectable, 2) borderline resectable, 3) locally advanced/unresectable, 4) adjuvant/resectable, and 5) palliative. For definitions of these scenarios, See Criteria Defining Resectability Status (PANC-B).**
- **Staging is optimally determined with modern contrast enhanced abdominal CT (3-D CT) and/or MRI imaging with thin cuts through the pancreas along with an EUS.**
- **If patients present with biliary obstruction (jaundice/elevated direct bilirubin), plastic or metal stents should be placed prior to initiation of RT. A percutaneous drain can also be used if ERCP stent placement is unsuccessful.**
- **The role of laparoscopic evaluation prior to chemoradiation is controversial, although standard at some institutions.**
- **Ideally, patients should be treated on clinical trials when available. Radiation is typically given concurrently with chemotherapy, except in the palliative setting, with intraoperative radiation therapy (IORT), or with stereotactic body radiation therapy (SBRT).**

Standard Recommendations:
**Note: It is not known whether one regimen is necessarily more effective than another; hence, these are given as examples of commonly utilized regimens, however, others based on similar principles are acceptable.

Neoadjuvant resectable/borderline resectable:

- **No standard treatment regimen currently exists for neoadjuvant resectable or borderline resectable pancreatic cancer. Neoadjuvant therapy for patients with resectable tumors should ideally be conducted on a clinical trial. Generally, use similar paradigms as for locally advanced unresectable disease.**
  - **Upfront flouropyrimidine- (CI-5-FU or capecitabine- based chemoradiation (CRT).[2,3]**
  - **Upfront gemcitabine-based CRT.[4]**
  - **Induction chemotherapy (2-4 cycles) followed by 5-FU- or gemcitabine-based CRT.[5]**

  Options include RT 45-54 Gy in 1.8-2.5 Gy fractions or 36 Gy in 2.4 Gy fractions.[6]
- **Ideally, surgical resection should be attempted 6-8 weeks following CRT. Surgery can be performed >8 weeks following CRT; however radiation-induced fibrosis may potentially make surgery more difficult.**

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PRINCIPLES OF RADIATION THERAPY

Unresectable/Locally advanced (non-metastatic):

- Upfront fluoropyrimidine (CI 5-FU or capecitabine)-based chemoradiation (CRT) in select patients.
- Upfront gemcitabine- based CRT in select patients.[7,8]
- Induction chemotherapy (2-4 cycles) followed by 5-FU or gemcitabine-based CRT.[9,10]

Options include:

- RT 45-54 Gy in 1.8-2.5 Gy fractions or
- 36 Gy in 2.4 Gy fractions.[11]

- Following CRT, additional maintenance chemotherapy is sometimes used, especially if tumors are still unresectable.
- In cases where 1) it is highly unlikely that patients will become resectable (complete encasement of superior mesenteric/celiac arteries) 2) there are suspicious metastases, and 3) patients may not be able to tolerate CRT, then it may be reasonable to start with chemotherapy (2-6 cycles) followed by definitive CRT if no evidence of metastatic progression.
- If patients present with poorly controlled pain or local obstructive symptoms, it may be preferable to start with upfront CRT.
- No standard total dose or dose per fraction has been established for SBRT; therefore, it should preferably be utilized as part of a clinical trial.[12]

Adjuvant:

- Treatment options following pancreaticoduodenectomy or distal pancreatectomy include:
  - Upfront fluoropyrimidine- (CI 5-FU or capecitabine) or gemcitabine-based chemoradiation followed by maintenance 5-FU or gemcitabine.[13]
  - Gemcitabine or CI 5-FU (1 cycle) followed by CI 5-FU/RT followed by maintenance gemcitabine or CI 5-FU.[14]
  - Gemcitabine or bolus 5-FU/leucovorin [15]
  - Gemcitabine or bolus 5-FU/leucovorin for 2-6 cycles followed by fluoropyrimidine- (CI 5-FU or capecitabine) based CRT.[16]

  RT 45-46 Gy in 1.8-2 Gy fractions to the tumor bed, surgical anastomoses, and adjacent lymph, followed by an additional 5-9 Gy to the tumor bed and anastomoses.[17]

Palliative:

- See Principles of Palliation and Supportive Care (PANC-C).
  - RT alone to the primary tumor plus a margin (Typically 30-36 Gy in 2.4-3.0 Gy fractions) is reasonable for patients with metastatic disease who require local palliation for obstruction or pain.[18]
  - Palliative RT can also be considered for patients who are elderly and/or not candidates for definitive therapy because of comorbidities.
  - Metastatic sites causing pain may also be palliated with RT.

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PRINCIPLES OF RADIATION THERAPY

Radiation Therapy Treatment Planning Principles

- Patients should undergo a CT simulation (thin slices through the pancreas/bed and locoregional nodal basins) with IV (assuming adequate kidney function) and oral contrast. For resected cases, preoperative CT scans and strategically- placed surgical clips are used to determine the tumor bed, ideally with the surgeon's assistance. In the neoadjuvant, borderline, and locally advanced settings the pancreatic gross tumor volume (GTV) and pathologic nodes (minimum >1 cm and/or FDG-avid on PET) are contoured with assistance from structural (CT/MRI) and functional imaging (PET). [19,20]
- The PTV should be defined per the ICRU-62 guidelines.[21] A GTV should be defined for intact pancreatic tumors. For adjuvant cases, a CTV includes high risk peri-pancreatic lymph nodes, anastomoses, pancreatic tumor bed derived from pre-surgical imaging and strategically-placed surgical clips. CTV expansions are needed to include possible microscopic disease. Further expansion to PTV includes ITV for target/breathing motion and additional margin for patient set-up error (SM).[22-24] Organs at risk (OARs) should also be contoured and evaluated in the DVH.
- Elective nodal irradiation (ENI) is commonly used for adjuvant cases but is controversial for unresectable/neoadjuvant/borderline resectable cases.[11] Standard margin expansions for unresectable cases include the gross tumor and any pathologic lymph nodes (GTV) plus a 0.5-1.5 cm margin to target microscopic extension (CTV) and an additional 0.5-2 cm volume to account for tumor/breathing motion and patient set-up errors (PTV). With these expansions, peri-pancreatic nodes are generally included. 3D-conformal or intensity modulated radiation therapy (IMRT) with breathhold/gating techniques can result in improved PTV coverage with decreased dose to organs at risk (OARs). [25,26] With SBRT, smaller margins are used (0.2-0.5 cm) and the PTV does not cover locoregional elective nodal regions.[27] If small GTV margin expansions are used for CTV and PTV, breathing motion and set-up error should be evaluated or controlled per the AAPM task group 76 guidelines.[28]
- IORT is delivered with electron beam radiation (IOERT) or high dose rate brachytherapy (HDR-IORT). IORT is generally delivered in a single fraction and in combination with adjuvant or neoadjuvant CRT. The role of IORT for unresectable and resectable cases is controversial but is ideally used in cases where resection may result in close or involved margins.[29]
- It is imperative to evaluate the DVH of the PTV and critical normal structures such as liver, kidneys, spinal cord, liver and bowel. (See Table 1. Normal Tissue Dose Volume Constraints [PANC-D, 4 of 6]) While these limits are empirical they differ based on dose per fraction, total dose delivered, and disease status (adjuvant vs. unresectable). Studies have shown that the tolerability of radiation is largely dependent on PTV size/elective nodal irradiation, types of concurrent systemic/targeted therapy, and whether conformal (3-D, IMRT, SBRT) vs. conventional radiation is used.

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PRINCIPLES OF RADIATION THERAPY

- **Fractionated RT is typically delivered as 30-60 Gy over ~3-6 weeks (1.8-3.0 Gy/fraction) with concurrent 5FU/capecitabine or gemcitabine as a radiosensitizer. For resected cases, 45 Gy is delivered to the tumor bed, surgical anastomosis, and regional lymph nodes. Additional radiation (~5-15 Gy) may be administered to the tumor bed/area of involved margins and anastomoses paying careful attention to dose to small bowel. For unresectable disease, 50-54 Gy in 1.8 to 2.0 cGy fractions is recommended. One must also use caution when multiple chemotherapeutic/targeted therapies are given concurrently with RT. For EBRT it is preferred that high energy photon beams are used. SBRT is often delivered in 1-5 fractions ranging from 5-25 Gy per fraction. IORT can be delivered in a single fraction alone (15-20 Gy) or in combination with EBRT (10-20 Gy).**
- **Several clinical trials (RTOG) now refer to atlases to assist with contouring and adjuvant RT planning (http://www.rtog.org/CoreLab/ContouringAtlases.aspx).**

Table 1: Normal Tissue Dose Volume Constraints

Structure	Unresectable/Preoperative Constraints	Adjuvant/Resected Constraints
Kidney (L & R)	Not more than 30% of the total volume can receive ≥ 18 Gy. If only one kidney is functional, not more than 10% of the volume can receive ≥18 Gy.	If two functioning kidneys present, not more than 50% of the right and 65% of the left kidney should receive >18 Gy. For IMRT planning mean dose to bilateral kidneys should be ≤18 Gy. If only one kidney is present not more than 15% should receive ≥18 Gy and no more than 30% should receive ≥14 Gy.
Stomach, duodenum, jejunum	Max dose ≤55 Gy; not more than 30% of the volume can be between 45 and 55 Gy.	Max dose ≤55 Gy; <10% of each organ volume can receive between 50-53.99 Gy. <15% of each organ volume can receive 45-49.99 Gy.
Liver	Mean dose cannot exceed 30 Gy.	Mean liver dose ≤25 Gy.
Spinal cord	Max dose to a volume of at least 0.03 cc must be ≤45 Gy.	Max dose ≤45 Gy.

*Adapted from RTOG 0936 (3-D conformal, 1.8-50.5) and RTOG 1102 (IMRT, 2.2 to 55 Gy)
**Adapted from RTOG 0848 (3-D or IMRT)

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Table 2. Commonly used radiation therapy abbreviations

3D-CRT	3-D Conformal Radiation Therapy
IMRT	Intensity Modulated Radiation Therapy
SBRT	Stereotactic Body Radiation Therapy
SABR	Stereotactic Ablative Radiotherapy
EBRT	External Beam Radiation Therapy
ENI	Elective Nodal Irradiation
IORT	Intraoperative Radiation Therapy
DVH	Dose Volume Histogram
GTV	Gross Tumor Volume
CTV	Clinical Tumor Volume
IM	Internal Margin: Variations in shape/size of CTV due to respiration and adjacent structures
ITV	Internal Target Volume: encompasses the CTV and IM. (ITV = CTV + IM)
PTV	Planning Target Volume
BED	Biologically Effective Dose
OAR	Organ At Risk
ABC	Airway Breathing Control
IGRT	Image Guided Radiation Therapy
4DCT	Four Dimensional Computerized Tomography
CBCT	Cone Beam Computerized Tomography

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PRINCIPLES OF CHEMOTHERAPY (1 of 3)

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

- **Acceptable monotherapy options include:**
  - **Gemcitabine at 1000 mg/m^2 over 30 minutes, weekly for 3 weeks every 28 days (category 1).**
  - **Fixed-dose rate gemcitabine (10 mg/m^2/minute) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B).**
  - **Capecitabine (category 2B)**
- **Acceptable chemotherapy combinations (for patients with good performance status):**
  - **Gemcitabine + erlotinib[1] (category 1)**
  - **FOLFIRINOX[2] (category 1)**
  - **Gemcitabine + capecitabine[3]**
  - **Gemcitabine + cisplatin (especially for patients with possible hereditary cancers)[4]**
  - **Fixed-dose rate gemcitabine, docetaxel, capecitabine (GTX regimen) (category 2B)[5]**
  - **Gemcitabine + nab-paclitaxel[6] (category 2B)**
  - **Fluoropyrimidine + oxaliplatin (category 2B) (eg, 5-FU/leucovorin/oxaliplatin[7] or CapeOx[8])**
- **Second-line therapy may consist of gemcitabine for those patients not previously treated with the drug. Other options include capecitabine (1000 mg/m^2 PO twice daily, days 1-14 every 21 days) or 5-FU/leucovorin/oxaliplatin[7] or CapeOx.[8] Results of the CONKO 003 trial demonstrated a significant improvement in overall survival with the addition of oxaliplatin to 5-FU /leucovorin.[7]**

Locally Advanced

- **Depending on performance status, mono- or combination systemic chemotherapy, as noted above, may be considered as initial therapy prior to chemoradiation for appropriate patients with locally advanced, unresectable disease. Patients should be evaluated for recovery from hematologic and non-hematologic toxicity prior to initiation of chemoradiation. Patients who progress with metastatic disease are not candidates for chemoradiation unless required for palliative purposes.**

See Adjuvant, Neoadjuvant, and Salvage on PANC-E 2 of 3

See References on PANC-E 3 of 3

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PRINCIPLES OF CHEMOTHERAPY (2 of 3)

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.[9]
- ESPAC-3 study results showed no significant difference in overall survival between 5-FU/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.[10]
- 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.[11]
- For patients who relapse after receiving adjuvant therapy, subsequent therapy may consist of gemcitabine or gemcitabine based-combination therapy for patients previously treated with fluoropyrimidine-based therapy, or fluoropyrimidine-based therapy (eg, 5-FU/leucovorin/oxaliplatin[7] or CapeOx)[8] for patients previously treated with gemcitabine-based therapy.

Neoadjuvant

- Although there is insufficient evidence to recommend specific neoadjuvant regimens, most neoadjuvant regimens incorporate RT and chemoradiation is preferred in this setting.

See Metastatic and Locally Advanced on PANC-E 1 of 3

See References on PANC-E 3 of 3

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PRINCIPLES OF CHEMOTHERAPY (3 of 3)
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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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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 in the United States, an estimated 43,140 people were diagnosed with pancreatic cancer, and approximately 36,800 people will die of pancreatic cancer.[1] This disease is the fourth most common cause of cancer-related death among U.S. men (after lung, prostate, and colorectal cancer) and women (after lung, breast, and colorectal cancer).[1] Its peak incidence occurs in the seventh and eighth decades of life.[1] Although incidence is roughly equal in both sexes, African Americans appear to have a higher incidence of pancreatic cancer than white Americans.[2] Furthermore, the incidence and mortality rates of pancreatic cancer in the United States have remained approximately the same over the past 2 decades.[3] In these NCCN Pancreatic Adenocarcinoma guidelines, only tumors of the exocrine pancreas are discussed; neuroendocrine tumors are not included (please see the NCCN Neuroendocrine Tumors Guideline).

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.[4-7] There is some evidence that increased consumption of red meat and dairy products is also associated with an elevation in pancreatic cancer risk,[8] although other studies have failed to identify dietary risk factors for the disease.[6] An increased body mass index is associated with increased risk of pancreatic cancer,[9-11] as are occupational exposure to chemicals such as beta-naphthylamine and benzidine[12] and heavy alcohol consumption.[4]

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.[13-15] 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.[16, 17] Chronic pancreatitis has also been identified as a risk factor for pancreatic

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cancer,[18, 19] and a more recent study demonstrated a 7.2-fold increased risk for pancreatic cancer for patients with a history of pancreatitis.[20] 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,[21-23] and familial excess of pancreatic cancer is associated with high risk.[6, 23] For example, a germline mutation of the *CDKN2A* (p16) gene has been reported in families with pancreatic cancer and melanoma.[24, 25] An excess of pancreatic cancer is also seen in families harboring *BRCA2* (breast cancer susceptibility gene-2) mutations,[26, 27] and particular mutations in the *PALB2* gene have recently been identified as possibly increasing pancreatic cancer susceptibility.[28] Asymptomatic individuals at high risk for pancreatic cancer (ie, those with first-degree relatives with pancreatic cancer) were assessed using endoscopic ultrasound (EUS) in the Cancer of the Pancreas Screening 2 (CAPS2) project.[29] Preinvasive pancreatic neoplasms were detected in 10% of high-risk patients suggesting that EUS may have a promising role in screening high-risk patients.[29] 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.[30, 31]

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.[32] 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 Adenocarcinoma Panel agree 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.[33, 34] Subsequent decisions regarding diagnostic management and resectability should involve multidisciplinary consultation, with reference to appropriate radiographic studies to evaluate the extent of disease.

Imaging Evaluations

CT is the most widely available and best-validated imaging modality for diagnosing and staging patients with pancreatic cancer.[35, 36] A pancreas CT protocol involves triphasic (ie, arterial phase, late arterial phase, and venous phase) cross-sectional imaging with thin slices using multidetector CT.[35, 37, 38] A rationale for triphasic CT is that the difference in contrast enhancement between the parenchyma and adenocarcinoma is highest during the late arterial phase, thereby providing a clear distinction between a hypodense lesion in the pancreas and the rest of the organ.

In addition to 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

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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 the 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.[39]

Studies have shown that 70%-85% of patients determined by CT imaging to have resectable tumors were able to undergo resection.[35, 37, 39-42] The criteria for defining resectable disease by CT favor specificity over sensitivity to avoid denying surgery to patients with a potentially resectable tumor.[35] Furthermore, the sensitivity of CT for small hepatic and peritoneal metastases is limited.

In cases where CT is not possible or contraindicated (eg, contrast allergy), magnetic resonance imaging (MRI) with contrast can be used to diagnose and stage pancreatic cancer,[43] 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.[43]

NCCN institutions vary in the use of additional staging technologies, such as endoscopic ultrasound (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.[33] 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 a 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.[44] 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%, respectively. In this study, the clinical management of 11% of patients with invasive pancreatic cancer was changed as a result of PET/CT findings. Nevertheless, the role of PET/CT in this setting is evolving and has not yet been established. PET/CT is not a substitute for high-quality contrast-enhanced CT, although it can be considered as an adjunct to a formal pancreatic CT protocol in high-risk patients. Non-contrast chest CT or chest X-ray (CXR) is recommended as part of the preoperative workup of patients without evidence of abdominal metastases to evaluate for the presence of pulmonary metastases.[45]

As previously mentioned, EUS may provide useful staging information in pancreatic cancer, particularly through assessment of certain types of vascular invasion.[46, 47] 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 is 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.[47, 48]

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Patients with a mass in the pancreas and evidence of metastatic disease should under biopsy confirmation, preferably at the metastatic site, before undergoing treatment.

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. It can be difficult to discriminate between benign and malignant strictures or stenosis; however, severe stenosis and marked proximal dilatation more often indicate malignancy.[49] 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. Liver function tests and chest imaging are also recommended. If studies are consistent with pancreatic cancer, then multidisciplinary consultation is recommended.

Restaging with high quality abdominal and chest imaging is also recommended following surgery of resectable disease before initiation of adjuvant therapy. It should also be performed after administration of each treatment modality when systemic chemotherapy is followed by chemoradiation in the adjuvant setting. In addition, such restaging with abdominal (pancreas protocol), pelvic, and chest imaging is also recommended following administration of neoadjuvant therapy and prior to surgical resection for patients with borderline resectable disease.

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 that may be missed even with the use of a pancreatic CT protocol.[50, 51] 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).[52] For example, preoperative serum CA 19-9 levels >100 U/mL (see discussion on Tumor-Associated Antigens, below) have been associated with a greater likelihood of advanced disease and an increased probability of a positive finding on staging laparoscopy.[53] In a recent prospective review of 838 patients who were diagnosed with resectable pancreatic tumors on imaging evaluation between 1999 and 2005, 14% were found to have unresectable disease (21% yield if only pancreatic adenocarcinoma was considered) following subsequent laparoscopy.[54] Characteristics associated with an increased laparoscopic yield of unresectable disease 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 sub-radiologic 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 or borderline resectable disease was debated by the Panel, and it is included as a category 2A recommendation for patients staged with

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resectable pancreatic cancer considered to be at increased risk of disseminated disease, 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. The Panel considers positive cytology from washings obtained at laparoscopy or laparotomy to be equivalent to M1 disease.[55]

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 carbohydrate antigen (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 Differential Diagnoses, below).[56] CA 19-9 may be undetectable in Lewis antigen-negative individuals.[57] Furthermore, CA 19-9 may be falsely positive in cases of benign biliary obstruction,[58, 59] and thus does not represent an appropriate baseline. Preoperative measurement of CA19-9 levels should therefore be performed after biliary decompression is complete and bilirubin is normal.

A low postoperative serum CA 19-9 level and a decrease in serial CA 19-9 levels following surgery have been found to correlate with survival for patients undergoing resection for pancreatic cancer.[60-63] In a 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).[60] 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.[64] However, data are conflicting regarding the predictive significance of CA 19-9 response following chemotherapy in patients with advanced disease.[64-68] The Panel recommends measurement of serum CA 19-9 level following surgery prior to administration of adjuvant therapy. Of note, 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 possible differential diagnoses of patients suspected of having pancreatic cancer.[69-73]

Autoimmune pancreatitis, a rare form of chronic pancreatitis also known as lymphoplasmacytic sclerosing pancreatitis, is a heterogeneous disease that can present with clinical and radiologic characteristics of pancreatic cancer, such as jaundice, weight loss, an elevated CA 19-9 level, and the presence of diffuse pancreatic enlargement, a pancreatic ductal stricture, or a focal pancreatic mass.[71, 74-76] A benign disease that can be effectively treated with corticosteroids, autoimmune pancreatitis must be distinguished from pancreatic cancer to avoid unnecessary surgery and prevent delay in the initiation of appropriate treatment.

The finding of increased serum immunoglobulin (Ig) G levels is supportive of a diagnosis of autoimmune pancreatitis, although an elevated level of serum IgG4 specifically is the most sensitive and specific laboratory indicator.[77] The classic appearance of the pancreas

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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.[75] Cardinal histologic features of autoimmune pancreatitis include prominent lymphocytic infiltration of the pancreatic parenchyma with associated fibrosis. Jaundiced patients with locally advanced disease should be reviewed for autoimmune pancreatitis, and IgG4 levels should be assessed.

Autoimmune pancreatitis can also be negative for IgG4 and can present with a large pancreatic mass, thus closely mimicking pancreatic adenocarcinoma. For patients with borderline resectable disease and 2 or 3 negative biopsies, a second-opinion is recommended. Alternative diagnoses should be considered, especially autoimmune pancreatitis, and a short course of steroid treatment may be an appropriate first approach. If no response is seen, the patient should undergo laparotomy for removal of the mass.

Pathology

Biopsy

Although a histologic diagnosis is not required before surgery, it is necessary before administration of neoadjuvant therapy and for patients staged with locally advanced and unresectable pancreatic cancer or metastatic disease. 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. 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.[78] In rare cases when an EUS-directed biopsy cannot be obtained from a borderline resectable patients, there are other acceptable methods of biopsy. For instance, intraductal biopsies can be obtained via endoscopic cholangioscopy[79]; a percutaneous approach[78] or laparoscopic biopsy[80] are other alternatives.

A negative biopsy should be confirmed by at least 1 repeat EUS biopsy. 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,[35] although alternative diagnoses should also be considered (see Differential Diagnoses, above). 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. In patients without obstructive jaundice at initial presentation, EUS-FNA is highly accurate and reliable for determining malignancy; in patients with obstructive jaundice and biliary stricture, EUS-FNA is less accurate.[33] 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.[81] 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 for clearly resectable patients 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.

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Specimen orientation, pathologic analysis, and reporting

A pathologic evaluation of the surgical specimen involves both the pathologist and the surgeon.[82, 83] 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.[84] 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 Adenocarcinoma Panel is in favor of pathology synoptic reports from the College of American Pathologists (CAP).[85]

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.[85]

The American Joint Committee on Cancer (AJCC) has developed staging criteria for adenocarcinoma of the pancreas.[86] 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).[87] 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.[86, 87] 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 that renders them unresectable despite the absence of evidence of metastatic disease); or (4) disseminated (see section on Criteria for Resection, below), and this system is 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.[86] There is wide variation in the reported R1 rates of pancreatoduodenectomy specimens,[83] because there is no uniform definition of microscopic margin involvement. This is especially true for the vascular / uncinate / retroperitoneal / posterior margin, which seems to be an area of variability among pathologists. Although several methods of specimen orientation and pathologic analysis have been described, there is no uniform consensus on a standardized protocol for the gross pathological examination of these specimens (ie, en face margins or radial margins).[82, 83, 88]

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Surgical Management

Criteria for Resection

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.[89] Early concerns about high mortality associated with various pancreatic resection procedures[90] have now been lessened by studies demonstrating an acceptably low (< 5%) mortality in experienced centers (see Effect of Clinical Volume, below).[91] Even under the most optimal conditions, however, the median survival of resected patients ranges from 15 to 19 months, and the actuarial 5-year survival rate is approximately 20%.[92] 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.[93-95] With respect to margin status, there is evidence for the converse statement – the survival benefits of an R1 resection may be comparable to definitive chemoradiation without surgery.[96]

The NCCN Panel recommends that decisions about diagnostic management and resectability always involve multidisciplinary consultation. Although it is clear that patients with visceral, peritoneal, or pleural metastases or with 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.[35] Using these criteria, tumors are classified as resectable; borderline resectable; or unresectable (eg, locally advanced or metastatic disease).

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 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.[35]

An analysis of 9,559 patients diagnosed with early-stage disease from 1995-2004 revealed that a high percentage (71.4%) of these patients with potentially resectable disease were not treated surgically and that patients were less likely to receive surgery at a low-volume center.[97] 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.[98, 99] 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. Unresectable tumors include those with distant metastases, nodal metastasis beyond the field of resection, SMA or celiac encasement greater than 180 degrees, unreconstructable SMV/portal occlusion, or aortic invasion or encasement.

The consensus of the Panel is that patients should be selected for surgery on the basis of curative intent as determined by the probability

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of obtaining R0 resection margins. Patients at high risk for positive surgical margins are not considered to be good candidates for an upfront resection. Furthermore, the Panel recommends that patient factors be considered when deciding whether a patient is a surgical candidate. Age of the patient, comorbidities, performance status, and frailty are all things to be discussed during the multidisciplinary review. Please refer to the NCCN Senior Adult Oncology guidelines for further discussion of the treatment of older patients.

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. If the tumor is found to be unresectable during surgery, the Panel recommends biopsy confirmation of adenocarcinoma at this time, if a biopsy was not performed previously.

Because tumors of the body and tail cause symptoms late in their development, they are usually advanced at diagnosis and are rarely resectable. Patients with tumors in the head of the pancreas, who usually present because of jaundice, are treated with open or laparoscopic pancreatoduodenectomy.[100] 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. 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 pancreatoduodenectomy is associated with higher perioperative mortality when done in the setting of hyperbilirubinemia.[101-103] 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.[104-110] In 1999, a retrospective study from Memorial Sloan-Kettering Cancer Center examined 240 consecutive pancreaticoduodenectomies where 53% of patients underwent preoperative biliary decompression.[111] This study found a statistical relationship between the use of preoperative drainage (irrespective of the method used) and increased postoperative complications, including death, compared to 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 as part of a neoadjuvant chemoradiation program.[112] 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 a nearly 2-fold increase in the rate of serious complications in the stented group (74% vs. 39%; relative risk in the surgery alone 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.[113] Based on these reports, most groups who perform resection first advocate selective use of decompression only in patients who are

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symptomatic or septic or in whom surgical resection is significantly delayed.

Patients who present with jaundice and potentially resectable disease require placement of a temporary stent along with antibiotic coverage if symptoms of cholangitis or fever are present. 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. Most Panel members endorse use of a plastic stent in this case, since such a patient may undergo surgery shortly thereafter and not require the longer patency time of a metal stent. If metal stents are used, short stents are preferred by some Panel members because they may be less likely to interfere with the subsequent resection.

For patients with jaundice undergoing neoadjuvant induction therapy before pancreatic resection, biliary decompression is necessary before initiation of therapy and appears to be well tolerated with minimal increase in perioperative morbidity. Placement of a stent is thus required prior to administration of neoadjuvant therapy for patients with jaundice and borderline resectable disease that is biopsy-positive.[114-116]

The Panel pointed out that stents are an evolving technology. The choice of stents includes plastic and metal; fully covered, partially covered, or uncovered; rigid or self-expanding (also see the discussion on stents in Biliary Obstruction, below). While any stent can become occluded, several groups have reported better patency with metal stents.[114-116] Metal stents are generally viewed as more permanent than plastic stents. Covered metal stents may give more durable patency, since the cover prevents tumor ingrowth,[117] but the reported differences between covered and uncovered stents are not dramatic.[117, 118]

Furthermore, migration is more of an issue with covered stents.[118] This issue has lead to the introduction of partially covered stents [119], though these stents may still migrate in a substantial number of patients.[120, 121] Most metal stents used today are self-expanding. Their small initial diameters make them easy to place, and their placement rarely requires dilation.[119] Several Panel members reported that their institutions use plastic stents in patients with short life expectancies (<3 months).[119] The Panel could not reach a consensus on which type of stent is best used in each preoperative circumstance, since level-1 evidence is lacking. A clinical trial is currently recruiting patients to compare metal and plastic stents for preoperative biliary decompression in patients with pancreatic cancer (ClinicalTrials.gov NCT01191814).

Pylorus Preservation

Reconstruction options for the stomach after pancreatoduodenectomy center on preservation of the pylorus. Traverso and Longmire[122] 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[123] reported no adverse affects of pylorus preservation; however, van Berge Henegouwen et al[124] reported longer nasogastric drainage times. In several randomized and nonrandomized studies,[125-129] 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 pancreatoduodenectomy remains an unproven but certainly acceptable alternative to classic pancreatoduodenectomy performed with antrectomy.

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Pancreatic Anastomosis

Efforts in this area have focused on preventing pancreatic leaks and fistulas, which are morbid and potentially lethal complications of pancreatoduodenectomy. Pancreaticojejunostomy has traditionally been the standard reconstruction and is the major focus of morbidity and mortality after pancreatoduodenectomy 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.[130] 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.[131, 132] 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.[133] Stents used in the 1930s and 1940s continue to be used today, but data suggests that they do not decrease leak rates.[134] Pancreatic fistula rates are similar among studies (ranging in most studies from 6% to 16%),[123, 132, 135] although the exact way to define a pancreatic leak in terms of volume and duration of drainage remains controversial.[136]

In addition to technical modifications, octreotide has been examined for its ability to decrease postoperative pancreaticojejunal leaks in patients undergoing pancreatic resections. However, octreotide did not decrease fistula rates when assessed in 2 prospective, randomized, double-blind, placebo-controlled studies (at the University of Texas MD Anderson Cancer Center and Johns Hopkins Hospital).[137, 138] Finally, the use of fibrin glue sealant does not appear to decrease the rate of pancreatic fistulas.[139]

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.[140] Both autologous and synthetic grafts were used for arterial and venous reconstructions. As morbidity from pancreatoduodenectomy 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 the University of Texas MD Anderson Cancer Center has championed this approach, arguing that because overall mortality from pancreatoduodenectomy 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.[141] Furthermore, long-term outcome is not significantly worse for patients undergoing venous resection during pancreatoduodenectomy compared to patients who receive standard pancreatoduodenectomy.[142] Although compelling, this approach has not been universally accepted. During the 1990s, several studies reported operative mortality of 0% to 16.5%, 3-year Kaplan-Meier survival of 12% to 23%, and median survival of 5 to 14 months in patients receiving vein resection.[143-146] A recent study found that properly selected patients with adenocarcinoma of the pancreatic head who required vein resection (n = 141) had a median survival of approximately 2 years that did not differ from those having standard pancreatoduodenectomy and was superior to historical patients believed to have locally advanced disease who did not receive surgical treatment.[147] Nevertheless, a few groups have recommended caution and only use vein resection for selected patients.

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Extended Lymphadenectomy

The role of lymph node dissection as a component of pancreatoduodenectomy has been explored. 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 in an attempt to regionally control disease.[148, 149] A standard lymphadenectomy in patients undergoing pancreatoduodenectomy entails removal of nodes at the duodenum and pancreas and on the right side of the hepatoduodenal ligament, the right side of the superior mesenteric artery, and the anterior and posterior pancreatoduodenal lymph nodes.[150] An extended lymphadenectomy is most commonly performed in the United States by removing not only the nodes removed in the standard procedure, but also the soft tissue in the retroperitoneum from the hilum of the right kidney to the left lateral border of the aorta on the right side, and from the portal vein to the origin of the inferior mesenteric artery on the left.[151]

Several prospective, randomized trials have addressed the role of lymphadenectomy in patients undergoing pancreatoduodenectomy. The Italian Multicenter Lymphadenectomy Group reported on a series of 81 patients randomly assigned to pancreatoduodenectomy with or without extended lymph node resection. Although the statistical power was low, this study did not support the concept that an extended lymphadenectomy was a good prognostic factor.[152] A larger randomized prospective trial was performed at Johns Hopkins Hospital from 1996 through 2001 to evaluate the role of extended lymph node dissections.[153] The group of patients who received the regional lymphadenectomy in addition to pancreatoduodenectomy had longer operation times, but overall median survival did not differ between the 2 groups at 1, 3, and 5 years.[153-155] Furthermore, a meta-analysis of randomized controlled trials comparing pancreatoduodenectomy with standard versus extended lymphadenectomy supports the conclusion that the extended procedure does not have any impact on survival.[156] In addition, patients undergoing extended lymphadenectomy have increased rates of postoperative diarrhea compared to patients undergoing the standard resection.[157]

In summary, the information to date does not show any survival advantage to performing a regional lymphadenectomy in addition to the standard pancreatoduodenectomy.[158] At this point in time, data suggest that nodal metastases are a marker of systemic disease and that their removal is unlikely to alter overall survival. One exception might be in the situation of an otherwise R0 resection with clinically positive adenopathy outside the standard field of dissection. Overall, outside of a clinical trial, a regional lymphadenectomy should not be considered as a routine part of the Whipple procedure, although consideration can be given to sampling of the aortocaval and common hepatic artery nodes, as those with positive nodes in these positions have inferior prognoses.[159, 160]

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 pancreatoduodenectomy less frequently, patients might have increased morbidity and mortality. In 1993, Edge and colleagues[161] assessed 223 pancreaticoduodenectomies from 26 U.S. hospitals, but they found that caseload did not correlate with mortality. However, surgeons who performed fewer than 4 resections over the 2-year period of the study had more complications. The group

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from Memorial Sloan-Kettering Cancer Center examined the issue in 1995 and found that in a cohort of 1,972 patients, high-volume centers in New York State had significantly less mortality than low-volume centers (4% versus 12.3%).[162] High volume was defined as more than 50 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. Several other studies have assessed regional outcomes with pancreatoduodenectomy from U.S. hospitals.[163-167] These studies have reported decreased mortality, hospital length of stay, and overall cost at higher volume centers (or with surgeons who perform the resections frequently) when compared with low-volume centers. Interestingly, this effect was also seen in reports from Canada and the Netherlands.[168-170]

The definitions of high and low volume varied among all these studies. However, a striking difference is seen when the mortality rates from pancreatoduodenectomy 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).[171] 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 pancreatoduodenectomy 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.[172] 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 (16.3%) and high-volume (3.8%) centers is seen for pancreatoduodenectomy, as compared to major surgery at any other site, further reinforcing the magnitude of the effect that high-volume centers can specifically have on pancreatic cancer outcomes.

A study involving 301,033 patients with pancreatic adenocarcinoma included in the National Cancer Data Base (NCDB) evaluated the treatment patterns of 1,667 hospitals over a 19-year period.[173] 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 36.9% 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.[173]

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

Adjuvant Therapy

Leucovorin Shortage

There is currently a shortage of leucovorin in the United States. There are no specific data to guide management under these circumstances, and all proposed strategies are empiric. The panel recommends several possible options to help alleviate the problems associated with this shortage. One is the use of levo-leucovorin, which is commonly used in Europe. A dose of 200 mg/m^2 of levo-leucovorin is equivalent to 400 mg/m^2 of standard leucovorin. Another option is for practices or institutions to use lower doses of leucovorin for all doses in all patients, since the panel feels that lower doses are likely to be as efficacious as higher doses, based on several studies. The QUASAR study found that

175 mg leucovorin gave similar survival and 3-year recurrence rates as 25 mg leucovorin when given with bolus 5-FU to patients as adjuvant therapy following R0 resections for colorectal cancer.[174] Another study showed no difference in response rate or survival in patients with metastatic colorectal cancer receiving bolus 5-FU with either high dose (500 mg/m^2) or low dose (20 mg/m^2) leucovorin.[175] Also, the Mayo Clinic and North Central Cancer Treatment (NCTTG) group determined that there was no therapeutic difference between the use of high (200 mg/m^2) or low (20 mg/m^2) dose leucovorin with bolus 5-FU in the treatment of advanced colorectal cancer, although 5-FU doses were different in the 2 arms.[176] Finally, if none of the above options are available, treatment without leucovorin would be reasonable. For patients who tolerate this without grade II or higher toxicity, a modest increase in 5-FU dose (in the range of 10%) may be considered.

Postoperative Therapy

In 1985, the Gastrointestinal Tumor Study Group (GITSG) initially reported that the median survival of patients undergoing pancreatoduodenectomy could be prolonged almost 2-fold by postoperative chemoradiation.[177, 178] 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 42%, compared with 15% in the control group.[177]

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.[179] At a median follow-up of 11.7 years, no statistically significant differences were observed in the different study arms with respect to progression-free survival or overall survival for the subset of patients with pancreatic cancer.[180]

Provocative but controversial results from the European Study Group for Pancreatic Cancer (ESPAC)-1 trial have been reported by Neoptolemos and colleagues.[181] 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 lack of attention to quality control for RT.[182-184] 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 intention-to-treat (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).[185] 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).[186] An absolute survival difference of 12.0% was observed between the two groups at 5 years (21% vs. 9%).[186]

The Radiation Therapy Oncology Group study RTOG 97-04 is a phase III study that evaluated post-operative adjuvant treatment of resected

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pancreatic adenocarcinoma using either gemcitabine or fluorouracil for 3 weeks before and 12 weeks after 5-FU-based chemoradiation for both groups.[187] This trial, which utilized daily fractionated radiotherapy, included prospective quality assurance of all patients, including central review of preoperative CT imaging and radiation fields.[188] 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 (hazard ratio = 0.80; 95% CI, 0.63-1.00; P=.05).

Whereas results from the RTOG trial suggest a possible small advantage for adjuvant therapy with gemcitabine over 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 2 groups were compared (median survival was 23.0 months and 23.6 months, respectively).[189]

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, in timing of imaging, and 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, and CONKO-001 excluded patients with high postoperative CA19-9 or CEA levels[185]). 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. The use of gemcitabine-based chemotherapy is frequently combined, sequentially, with 5-FU based chemoradiation. Results of a recent randomized phase II trial suggest that gemcitabine-based chemoradiation may also be an effective adjuvant approach for patients with R0 resections.[190] Thus gemcitabine- or fluoropyrimidine-based chemoradiation with additional gemcitabine or 5-FU/leucovorin[189] chemotherapy, as well as chemotherapy alone with gemcitabine (category 1) or 5-FU/leucovorin (category 1) are listed in the guidelines as options for adjuvant treatment. It was the consensus of the Panel that when chemotherapy alone is the choice of adjuvant therapy, gemcitabine is preferred over 5-FU/leucovorin for most patients due to its more favorable toxicity profile. In the adjuvant setting, capecitabine is also listed in the guidelines (category 2B). Capecitabine should only be used in this setting as a last choice in patients for whom other options are inappropriate or unacceptable. The Panel considered capecitabine a reasonable alternative to 5-FU/leucovorin in this setting.

Although the optimal combination and sequencing of adjuvant RT has yet to be defined, the NCCN Panel recommends that postoperative RT, when given, should be administered at a dose of 45 to 46 Gy (1.8-2.0 Gy/day) with high energy photons (>4 MV) to the tumor bed, surgical anastomoses, and adjacent lymph node regions, followed by an additional 5-15 Gy to the tumor bed while paying careful attention to dose to the small bowel.[191, 192] The Panel strongly recommends use of CT simulation and 3-D treatment planning (thin slices through the pancreas/bed and locoregional basin) with intravenous (assuming adequate kidney function) and oral contrast. Treatment volumes should be based on preoperative CT scans and surgical clips (when placed). Radiation is usually given in combination with continuous infusion 5-FU,

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capecitabine, or gemcitabine, and can be given before or after systemic chemotherapy in the adjuvant setting. While no studies have demonstrated superiority of giving chemoradiation before versus after chemotherapy, when patients have a margin-positive resection, upfront chemoradiation followed by systemic chemotherapy is an appropriate option.[187, 191, 193]

Patients who have received neoadjuvant chemoradiation or chemotherapy are candidates for additional chemotherapy following surgery. 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. It is recommended that the patient undergo a pretreatment baseline assessment following surgery, including CT scan and CA 19-9 level, 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.

Intensity-modulated radiotherapy (IMRT) is increasingly being applied for therapy of pancreatic adenocarcinoma in the adjuvant setting with the aim of increasing radiation dose to the gross tumor/tumor bed while minimizing toxicity to surrounding tissues.[194] Results of a recent study demonstrated that IMRT resulted in reduced grade 3/4 toxicities when compared to patients who received a similar 5-FU-based regimen with 3-D conformal radiation in the RTOG 97-04 trial.[187, 195] Comparing the 2 trials, rates of grade 3/4 nausea and vomiting were 0% vs. 11% ($p = 0.024$) and of grade 3/4 diarrhea were 3% vs. 18% ($p = 0.017$),[195] suggesting that IMRT may be well tolerated and allow for higher radiation doses to the tumor.[195] There is no clear consensus on the appropriate maximum dose of radiation when IMRT technique is used.

Intraoperative radiation therapy (IORT) is sometimes used in resectable cases and may be best when resection may result is close or involved margins.[196] IORT is delivered with electron beam radiation (IOERT) or high dose rate brachytherapy (HDR-IORT). It is generally delivered in a single fraction of 15-20 Gy and in combination with adjuvant or neoadjuvant chemoradiation therapy. IORT can also be delivered in combination with external beam radiation therapy (EBRT, 10-20 Gy).

Preoperative (Neoadjuvant) Therapy

Novel contemporary approaches to adjuvant therapy have focused on preoperative (neoadjuvant) therapy for patients with borderline resectable disease with the goal of improving overall survival.[197, 198] The putative benefits of neoadjuvant therapy include increasing the likelihood that a higher proportion of resectable patients will receive chemotherapy and/or radiation, the potential to downsize tumors so as to increase the likelihood of a margin-free resection (ie conversion of borderline resectable patients), the potential to select for surgery those patients with more stable disease or disease that is more responsive to therapy, and the treatment of micrometastases at an earlier stage.[99, 199-201]

Neoadjuvant therapy in resectable disease

A number of studies have evaluated the use of neoadjuvant chemoradiation in patients with resectable disease.[198, 199, 202-209] A retrospective review of the collective experience at the University of Texas MD Anderson Cancer Center suggested that the use of preoperative chemoradiation therapy in patients with resectable disease is advantageous.[202] The authors suggest that preoperative therapy gives a selection advantage, in that approximately 25% of patients who are restaged after therapy are found to have progressive disease and are therefore spared the morbidity of a surgical procedure

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that would not benefit them.[202] In this analysis of 132 consecutive patients, the University of Texas MD Anderson Cancer Center group reported that combined preoperative chemoradiation and pancreatoduodenectomy yielded a median survival of 21 months, and 32% of patients were alive without evidence of disease at a median follow-up of 14 months.[202]

Although most studies investigating the neoadjuvant experience in patients with pancreatic cancer are retrospective, several small phase II studies have been published. In a randomized phase II trial evaluating the safety and efficacy of gemcitabine-based chemotherapy regimens as neoadjuvant therapy for patients with resectable pancreatic cancer, more patients receiving combination therapy were able to undergo resection compared with those in the gemcitabine only arm.[206]

In a prospective trial, preoperative radiation with concurrent gemcitabine was administered to 86 patients with resectable disease, and patients were restaged 4 to 6 weeks following completion of neoadjuvant treatment.[210] Although all patients were able to complete neoadjuvant therapy, at the time of restaging, 73 (85%) patients were able to undergo surgery; the majority of the remaining patients were precluded from undergoing a pancreatoduodenectomy 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.[115] In this study, which enrolled 90 patients, 79 patients were able to complete neoadjuvant therapy and 52 patients underwent surgery. 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.[200] These results provide support for restaging patients with abdominal (pancreas protocol), pelvic, and chest imaging and diagnostic laparoscopy before committing them to laparotomy after neoadjuvant therapy.

Although evidence suggests that there may be a better chance of margin-negative resection with preoperative therapy,[211] results of randomized trials addressing this issue have yet to be reported. A randomized phase II trial comparing preoperative chemoradiation to postoperative chemotherapy in patients with resectable pancreatic cancer is currently recruiting patients (Clinicaltrials.gov NCT00335543). At this time, the Panel does not recommend neoadjuvant therapy for resectable patients, except on a clinical trial.

Neoadjuvant therapy in borderline resectable disease

The use of neoadjuvant therapy in the setting of borderline resectable disease is a highly debated topic. Although there is no high-level evidence supporting its use, many NCCN centers prefer an initial approach involving neoadjuvant therapy, as opposed to immediate surgery, for patients with borderline resectable disease, and the Panel recommends neoadjuvant therapy as an option (category 2B) to upfront resection following clinical staging of disease as borderline resectable (see Criteria for Resection, above, for definition of borderline resectable disease). Several trials have shown that preoperative treatment of borderline resectable pancreatic adenocarcinoma can be effective and well-tolerated. A phase I/II trial of neoadjuvant therapy in borderline resectable disease allowed 4 of 26 patients (15%) to be resected.[212] A randomized phase II trial comparing 2 different neoadjuvant regimens in borderline resectable disease terminated early due to poor accrual, but 5 of 21 patients (24%) were resected.[213] In 2 recently published retrospective reviews, 31-35% of borderline resectable patients who completed neoadjuvant therapy had R0 resections.[214, 215]

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It is important to note that no randomized phase III trials have compared the approach of neoadjuvant therapy in borderline resectable disease compared to the approach of taking these patients to surgery without initial therapy and that the best regimens to use in the borderline neoadjuvant setting are unknown. A phase II clinical trial is currently underway (clinicaltrials.gov NCT01268384) to determine the R0 resection rate following neoadjuvant chemotherapy with fixed dose rate (FDR) gemcitabine and capecitabine in patients with borderline resectable or unresectable locally advanced disease. Additional randomized trials are needed.

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. Furthermore, patients for whom neoadjuvant therapy is planned should be assessed for jaundice, and placement of a stent is recommended prior to initiation of neoadjuvant therapy in patients with jaundice.[114-116]

Although there is insufficient evidence to recommend specific neoadjuvant regimens, most neoadjuvant regimens incorporate RT, and chemoradiation is preferred in this setting. Neoadjuvant therapy regimens are often similar to those used to treat locally advanced disease (see section on Chemoradiation for Locally Advanced Disease, below) and include upfront continuous infusion 5-FU- or capecitabine-based chemoradiation,[201, 216] upfront gemcitabine-based chemoradiation,[210] or 2 to 4 cycles of induction chemotherapy followed by 5-FU- or gemcitabine-based chemoradiation.[115] Options for radiation include 45-54 Gy in 1.8-2.5 Gy fractions or 36 Gy in 2.4 Gy fractions.[208] Abdominal (pancreas protocol), pelvic, and chest imaging should be repeated following neoadjuvant therapy, and surgical resection should only be attempted if there is a high likelihood of achieving an R0 resection. Surgery should be performed 6 to 8 weeks following therapy. Surgery can be performed more than 8 weeks following therapy, but radiation-induced fibrosis may potentially make surgery more difficult.

Chemoradiation for Locally Advanced Disease

Chemoradiation is a conventional option for the management of unresectable locoregional pancreatic cancer, although the utility of chemoradiation in this population of patients is controversial.[217] The role of chemoradiation was initially defined in a trial conducted by GITSG.[178] 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 2-fold 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.

Gemcitabine has also been used as a radiation sensitizer.[115, 210, 218-220] There is evidence to suggest that concurrent gemcitabine and radiation can yield similar outcomes when compared with 5-FU-based chemoradiation,[219, 221] 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 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.[222]

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Some studies have addressed the use of chemoradiation with or without chemotherapy to convert selected patients with locally unresectable disease to a resectable status.[197-199, 201, 223] In some instances, patients are converted to what appears to be a resectable status by radiographic characterization after completing treatment. Following resection, these patients have similar survival rates as those initially determined to be resectable.[224]

Following biopsy confirmation of adenocarcinoma and treatment for jaundice if present (a permanent metal stent is preferred in this situation), the Panel recommends chemoradiation for patients with locally advanced unresectable disease and good performance status and with no metastases. For primary definitive chemoradiation therapy, the NCCN recommends one of two options: 1) 45-54 Gy in 1.8-2.5 Gy fractions for 5-FU-based chemoradiation regimens or 2) 36 Gy in 2.4 Gy fractions for gemcitabine-based chemoradiation regimens.[219] Use of CT simulation and 3-D treatment planning is strongly encouraged. Treatment volumes should be based on CT scans and surgical clips/fiducials (when placed). Radiation is given with concurrent gemcitabine,[219, 225, 226] capecitabine, or continuous infusion 5-FU.[221] Currently, upfront chemoradiation[225, 226] or, preferably, systemic chemotherapy followed by consolidation chemoradiation therapy[227-229] are recommended options for patients with unresectable disease and good performance status. When induction chemotherapy is administered, laparoscopy is sometimes performed to evaluate distant disease before chemoradiation therapy is initiated. If patients develop metastatic disease during systemic chemotherapy, chemoradiation is not given, as patients with metastatic disease are not candidates for chemoradiation unless required for palliation. Furthermore, patients should be evaluated for recovery from hematologic and non-hematologic toxicity prior to initiation of chemoradiation. When systemic chemotherapy precedes administration of chemoradiation, the Panel also recommends restaging with a CT scan prior to radiation therapy. 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. Following chemoradiation therapy, additional maintenance chemotherapy is sometimes used, especially if tumors are still unresectable.

The choice between upfront chemoradiation versus induction chemotherapy followed by consolidation chemoradiation is based on disease characteristics. If patients present with poorly controlled pain or local obstructive symptoms, it may be preferable to start with upfront chemoradiation therapy. Three phase II trials have assessed the upfront chemoradiation approach in locally advanced pancreatic adenocarcinoma, with median survival rates ranging from 8.2 to 9 months.[225, 230-232]

Another option is to start with 2 to 6 cycles of chemotherapy in cases where 1) it is highly unlikely that the patient will become resectable (ie, complete encasement of superior mesenteric/celiac arteries), 2) there are suspicious metastases, or 3) the patient may not be able to tolerate chemoradiation. If there is no evidence of metastatic progression, definitive chemoradiation can follow. This treatment approach, employing an initial 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.[227] This approach is currently being evaluated in an ongoing phase III trial (GERCOR-LAP-07-D07-1; ClinicalTrials.gov NCT00634725), comparing gemcitabine with or

without erlotinib followed by the same chemotherapy or capecitabine-based chemoradiation with or without erlotinib.

Intensity-modulated radiotherapy (IMRT) is increasingly being applied for therapy of locally advanced pancreatic adenocarcinoma with the aim of increasing radiation dose to the gross tumor while minimizing toxicity to surrounding tissues.[233-235] A retrospective treatment planning study evaluated the dose escalation that might have been possible in 15 patients with locally advanced unresectable pancreatic adenocarcinoma had IMRT been used instead of 3-D conformal planning.[235] While the authors concluded that the IMRT plans would allow for significant increase in target volume dose with substantial dose reductions to local organs at risk,[235] there is no clear consensus on the appropriate maximum dose of radiation when IMRT is used.

Stereotactic body radiotherapy (SBRT) is another technique aimed at increasing dose to the gross tumor while sparing radiation to nearby healthy tissue. Retrospective analysis of 77 patients with unresectable disease demonstrates that while SBRT gives effective local control, it lends no improvement to overall survival and is associated with significant toxicities.[236] There is also no standard total dose or dose per fraction established for SBRT, and the Panel currently recommends that SBRT only be utilized as part of a clinical trial.[236]

Chemotherapy without radiation therapy is also an option for patients with locally advanced pancreatic cancer, especially for patients with poor performance status (see Chemotherapy for Locally Advanced or Metastatic Disease, below, for a discussion of the different chemotherapy options). Results of 2 early randomized trials comparing chemoradiation to chemotherapy in locally advanced disease were contradictory.[237, 238] A phase III randomized trial (ECOG-4201) that 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=0.044).[226] 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.[239] In this study, gemcitabine alone was associated with a significantly increased overall survival rate at 1 year compared with chemoradiation (53% vs. 32%; HR = 0.54, 0.31–0.96; P = 0.006). This study was stopped before the planned accrual, because an interim analysis revealed that patients in the chemoradiation arm had a lower survival rate. Also, patients in the chemoradiation arm experienced severe toxicity and were more likely to receive a shorter course of maintenance therapy with gemcitabine, suggesting that the observed differences in survival were most likely attributable to the extreme toxicity of this particular chemoradiation regimen.

It is important to reiterate that biopsy confirmation of pancreatic adenocarcinoma be obtained before treatment. At least 2 or 3 negative biopsies should be obtained before entertaining alternative diagnoses (see Differential Diagnoses, above). A second opinion should also be obtained in such a case. Occasionally, other cancer types are confirmed, and the patient should be treated according to the appropriate NCCN Guideline.

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Chemotherapy for Locally Advanced or Metastatic Disease

Leucovorin Shortage

There is currently a shortage of leucovorin in the United States. Please see the discussion in the section on Adjuvant Therapy, above, for a detailed discussion.

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 0-1, with good pain management, patent biliary stent, and adequate nutritional intake). Patients who present with very poor performance status may benefit from the administration of gemcitabine (category 1 recommendation), 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 and celiac block for pain (see Palliation of Locally Advanced and Metastatic Disease, below, and Principles of Palliation and Supportive Care in the guidelines). Of note, debilitated patients with advanced disease may have abrupt changes in clinical status. Therefore, if treatment is begun, it should proceed with close follow-up. Patients may experience sudden onset of bleeding or thromboembolism, rapidly escalating pain, biliary stent occlusion, cholangitis, or other infections. Moreover, clinically meaningful tumor progression may develop quickly, and tumor-related symptoms may be inappropriately attributed to chemotherapy or other causes. For instance, patients who complain of intractable nausea and vomiting may have gastric outlet obstruction rather than chemotherapy-induced emesis. Peritoneal carcinomatosis may manifest as ascites or in its more subtle form, as abdominal bloating, decreased oral intake, and constipation.

FOLFIRINOX

In 2003, a French group reported the results of an open phase I study to assess the feasibility of a combination therapy consisting of 5-FU/LV plus oxaliplatin and irinotecan (FOLFIRINOX) for the treatment of patients with metastatic solid tumors.[240] Their study included 2 patients with pancreatic cancer and showed anti-tumor activity. A subsequent multicenter phase II trial specifically for patients with advanced pancreatic adenocarcinoma demonstrated promising response rates.[241] A later randomized phase II trial showed a response rate of >30% to FOLFIRINOX in patients with metastatic pancreatic cancer.[242]

Results from the recently presented preplanned interim analysis of the randomized phase III PRODIGE 4/ACCORD 11 trial evaluating the regimen of 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. 3.4 months; P<0.0001) and median overall survival (10.5 months vs. 6.9 months; P<0.001), in favor of the group receiving FOLFIRINOX.[243] Because of these strong results, the Panel has added FOLFIRINOX as a category 1 recommendation for first-line treatment of good performance status patients with either metastatic or locally advanced unresectable disease.

There are, however, some concerns about the toxicity of the FOLFIRINOX regimen. The grade 3/4 toxicity rates were 12.3% for diarrhea, 15.6% for nausea, 17.2% for vomiting, 24% for fatigue, 47.9%

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for neutropenia, and 5.7% for febrile neutropenia.[243] Despite the high levels of toxicity, no toxic deaths have been reported.[241-243]

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.[244] The NCCN Panel recommends gemcitabine monotherapy (1,000 mg/m^2 over 30 min, weekly for 3 weeks every 28 days) as one option for front-line therapy for patients with metastatic disease (category 1).[244] The NCCN Panel also recommends gemcitabine monotherapy as an option for patients with unresectable, locoregional disease and a good performance status (category 2A). 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, below).

Because the approved indications for gemcitabine include the relief of symptoms, the Panel recommends gemcitabine as a reasonable option for symptomatic patients with metastatic or locally advanced unresectable disease with poor performance status (category 1). An alternative option for these patients is best supportive care.

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] 350 mg/m^2/minute) maximizes intracellular concentrations of the phosphorylated forms of gemcitabine.[245] In a randomized phase II trial, the infusion of gemcitabine at a FDR led to better survival compared with gemcitabine delivered at a higher dose, over 30 minutes.[246] 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.[247] 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] and GTX [gemcitabine, docetaxel, and capecitabine], see Gemcitabine Combinations, below).[248, 249]

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).[247-260]

Recommended combinations are discussed below. However, the Panel does not consider the combination of gemcitabine plus docetaxel[261] or

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gemcitabine plus irinotecan[260-262] to meet criteria for inclusion in the guidelines.

Gemcitabine plus cisplatin

Data regarding the survival impact of combining gemcitabine with a platinum agent are conflicting, and results of randomized controlled 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 versus gemcitabine alone in patients with advanced pancreatic cancer failed to show a significant survival benefit for the combination over the single agent.[251, 252, 255] 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.[258] 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.[247]

Nevertheless, selected patients may benefit from this regimen since patients with breast and ovarian cancers who are carriers of a *BRCA* mutation,[263, 264] and selected patients with inherited forms of pancreatic cancer[26] may have disease that is particularly sensitive to a platinum agent. A retrospective study from Johns Hopkins University School of Medicine 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.[265] Patients with a family history of pancreatic cancer alone demonstrated a large survival advantage when treated with platinum-based chemotherapy (6.3 vs. 22.9 months, HR 0.34, 95% CI 0.15-0.74; $p < 0.01$).[265] Further, gemcitabine plus cisplatin may be a good choice in selected patients with disease characterized by hereditary risk factors (eg, *BRCA* or *PALB2* mutations). The Panel recommends gemcitabine plus cisplatin for metastatic patients, especially those with possible hereditary cancers, as a category 2A recommendation.

Gemcitabine plus fluoropyrimidine

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.[250] 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.[253] 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.[257] Although there are concerns about dosing and toxicity of capecitabine in a U.S population, results from a recent phase I 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.[266] Of note, results from several studies have indicated that the benefit of gemcitabine combination chemotherapy is predominantly seen in patients with good performance status.[254, 255, 257]

The NCCN Panel considers gemcitabine-based combination therapy with capecitabine to be a reasonable option (category 2A) 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.

Gemcitabine plus erlotinib

Although phase II trial results of gemcitabine combined with new targeted drugs (eg, bevacizumab, cetuximab) were encouraging,[267, 268] 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.[269-273] Results of the Cancer and Leukemia Group B (CALGB) phase III trial, which evaluated gemcitabine and bevacizumab (an anti-VEGF [vascular endothelial growth factor] antibody) compared with gemcitabine plus placebo in patients with locally advanced or metastatic pancreatic cancer, and the Southwest Oncology Group (SWOG) phase III randomized trial, which assessed cetuximab (which targets the epidermal growth factor receptor [EGFR]) plus gemcitabine versus gemcitabine alone did not reveal improvements in survival upon addition of the biologic agent.[270, 271, 273] A recent phase III trial comparing gemcitabine and erlotinib with or without bevacizumab in patients with metastatic pancreatic cancer, bevacizumab did not improve overall survival, although a significant improvement in progression-free survival was observed with the addition of bevacizumab to the gemcitabine/erlotinib combination.[272]

However, in a phase III double-blind, placebo-controlled 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.[269] 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, but most were grade 1 or 2.[269]

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 1).

Gemcitabine plus nab-paclitaxel

The Panel includes the combination of gemcitabine plus nab-paclitaxel as a category 2B recommendation for the treatment of patients with advanced disease and good performance status. Nab-paclitaxel is an albumin-bound nanoparticle form of paclitaxel. In a recent report of a phase I/II trial in which 63 patients received gemcitabine plus nab-paclitaxel, 23% of patients had complete responses, 55% had partial responses, and 8% showed stable disease.[274] At the time of publication, the median survival had not been reached.

GTX regimen

The Panel included the combination of gemcitabine, docetaxel, and capecitabine (GTX regimen) as a category 2B recommendation for the treatment of patients with advanced disease and good performance status. In a report of 35 patients with metastatic pancreatic cancer treated with this regimen, the authors reported an overall response rate of 29% (all had partial responses), with an additional 31% of patients

exhibiting a minor response or stable disease.[249] The median survival was 11.2 months for all patients and 13.5 months for patients exhibiting a partial response. This regimen demonstrated significant toxicities, however, with 14% of patients having grade 3/4 leukopenia, 14% having grade 3/4 thrombocytopenia, and 9% with grade 3/4 anemia.

Capecitabine

The Panel lists capecitabine monotherapy as a first-line treatment option for patients with locally advanced unresectable or metastatic disease (category 2B). This recommendation is supported by a randomized phase III trial from the Arbeitsgemeinschaft Internistische Onkologie (AIO) group in which overall survival was similar in patients with advanced pancreatic cancer receiving either capecitabine plus erlotinib followed by gemcitabine monotherapy or gemcitabine plus erlotinib followed by capecitabine monotherapy.[275]

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. As many as 50% of them will continue to maintain a sufficiently good performance status to consider second-line therapy.[276] Enrollment in a clinical trial is the preferred course of action for these patients. For patients previously treated with fluoropyrimidine-based therapy, gemcitabine is an alternative that may offer palliative benefits in the second-line setting.[277] For patients who have received prior gemcitabine-based therapy, fluoropyrimidine-based chemotherapy regimens are acceptable options.[278-280] The Panel includes capecitabine, 5-FU/LV/oxaliplatin[281], and CapeOx[280] as options. Note that the capecitabine dose (1,000 mg/m^2 PO twice daily) recommended in the guidelines 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).[282] 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,[281, 283] 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, 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. When this period is greater than 6 months, systemic therapy as previously administered or an alternative systemic regimen is recommended. Recommended regimens are as for second-line therapy in metastatic disease (also see Principles of Chemotherapy in the guidelines). In all cases of recurrent disease, a clinical trial is the preferred option; best supportive care without salvage therapy should also be an option, especially for patients with poor performance status.

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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 III trials to show clinically significant benefit for patients with pancreatic cancer, and to address the importance of integrating basic and clinical knowledge in the design of clinical trials 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.[284]

- 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 efficacy of the agent (ie, vaccines in patients with early-stage disease).
- Phase III trials should not be initiated in the absence of clinically meaningful efficacy and safety signals in the phase II setting.
- Phase II and III clinical trials should have a primary 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 are, in many respects, 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. The main objective of palliative care is to prevent and ameliorate suffering, while ensuring optimal quality of life. Palliative surgical procedures are best reserved for patients with longer life expectancies.

Biliary Obstruction

Approximately 65%-75% of patients with pancreatic cancer develop symptomatic biliary obstruction.[285] 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

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recommended unless biliary bypass is performed (also see the discussion on stents in Preoperative Biliary Drainage, above). 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 a covered self-expanding metal stent inserted endoscopically indicated that median patency times were 1.8 and 3.6 months (P=0.002), respectively.[286] A metaanalysis comparing metal and plastic biliary stents placed endoscopically in patients with pancreatic adenocarcinoma characterized by biliary obstruction showed similar results.[287] This study 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.

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.[288] Durable palliation of biliary obstruction can often be achieved with an expandable metallic biliary endoprosthesis (eg, Wallstent, Boston Scientific) in this situation.[288]

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. The Panel recommends stenting or an open biliary-enteric bypass with or without duodenal bypass (category 2B for prophylactic duodenal bypass) and with or without open ethanol celiac plexus block (category 2B). Bypass of the common bile duct (choledochojejunostomy) or common hepatic duct (hepaticojejunostomy) to the jejunum is preferred to bypass of the gallbladder (cholecystojejunostomy) since choledochojejunostomy / hepaticojejunostomy provide more durable and reliable palliation of biliary obstruction.[285] Furthermore, the Panel recommends biopsy confirmation of adenocarcinoma during surgery when the tumor is found to be unresectable, if a biopsy was not performed previously.

Biliary decompression is also required for jaundiced patients with disease progression precluding surgery with or without neoadjuvant therapy. Here, stenting or biliary bypass is recommended, with or without duodenal bypass (category 2B for prophylactic duodenal bypass) and with or without open ethanol celiac plexus block (category 2B). One final circumstance requiring biliary drainage is in jaundiced patients with locally advanced or metastatic disease. In this situation, a permanent metal stent is preferred, unless biliary bypass was performed at the time of laparoscopy or laparotomy. However, several Panel members reported that their institutions use plastic stents in patients with short life expectancies, due to the lack of concern about long-term patency.

Gastric Outlet Obstruction

Symptomatic gastric outlet obstruction occurs in 10%-25% of patients with pancreatic cancer.[285] Patients with locally advanced or metastatic disease and a short life expectancy or poor performance status who develop gastric outlet obstruction may be palliated with an endoscopically placed enteral stent.[288] An alternative for these patients

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with poor performance status is percutaneous endoscopic gastrostomy (PEG) tube placement. For a fit patient with a life expectancy greater than 3 to 6 months (i.e., locally advanced disease) who develops gastric outlet obstruction, an open or 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 an enteral stent.[289-291] Nevertheless, placement of an enteral stent is also an option for these patients.

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 have unresectable cancers 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.[292, 293] 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.[294] 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.[294, 295] Minimally invasive techniques including EUS-guided (preferred if available) and percutaneous fluoroscopic- or CT-guided celiac plexus neurolysis are recommended, 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, palliative radiation therapy may be considered, even in the setting of metastatic disease, if not already given as part of primary therapy. In such cases, radiation is given with or without concurrent chemotherapy to the primary tumor plus a margin (typically 30-36 Gy in 2.4-3.0 Gy fractions) or radiation alone to the metastatic site.

Additional Palliative Interventions

Pancreatic insufficiency

Exocrine enzyme insufficiency in pancreatic cancer is caused by tumor-induced damage to the pancreatic parenchyma and/or blockage of the pancreatic duct, as well as by surgical removal of pancreatic tissue, and results in an inadequate production of digestive enzymes.[296, 297] This deficiency in pancreatic enzymes results in inadequate absorption of fat, carbohydrates, and proteins, leading to steatorrhea, abdominal cramps, weight loss, and malnutrition.[298] Oral pancreatic exocrine

enzyme replacement therapy is recommended for patients with pancreatic cancer who have symptoms of exocrine enzyme deficiency. Because pancreatic insufficiency occurs in up to 94% of patients undergoing pancreatic surgery,[299, 300] therapy may be initiated without diagnostic tests. Enteric-coated mini-microspheres containing preparations of pancreatic enzymes are taken orally (25,000 to 75,000 units of lipase for a main meal and 10,000 to 25,000 units of lipase for a snack, depending on fat content), with half of the dose taken at the start of the meal and half taken in middle of the meal.[298] For patients failing this therapy, doses of the enzyme preparation can be increased, and inhibition of gastric secretion with a proton pump inhibitor can also be considered.[298, 299] Patients with a clinical suspicion of pancreatic insufficiency despite appropriate replacement may need a more thorough nutritional evaluation.

Treatment of thromboembolic disease

The risk of developing venous thromboembolic disease is substantially increased in patients with pancreatic cancer.[301] The Panel recommends low molecular weight heparin (LMWH) as preferred therapy over warfarin for patients with pancreatic cancer who develop a venous thromboembolism (VTE). 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.[302] In the CONKO 004 trial, VTE- and chemotherapy-naïve patients with advanced pancreatic cancer were randomized to receive palliative chemotherapy with or without the LMWH, enoxaparin.[303] 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. 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 are 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 to 6 months for 2 years, then annually. CA 19-9 determinations and follow-up CT scans every 3 to 6 months for 2 years after surgical resection are category 2B recommendations, 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

Resection remains the only chance for a cure of pancreatic adenocarcinoma, and resectable patients should under surgery without delay, followed by adjuvant therapy. Borderline resectable patients can undergo neoadjuvant therapy (category 2B) in the hopes of conversion to resectability. Patients with locally advanced unresectable disease and good performance status can undergo chemotherapy and chemoradiation with salvage therapy if performance status is

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maintained after progression. Good performance status patients presenting with metastatic disease can undergo palliative chemotherapy and can undergo salvage therapy if performance status is maintained after progression.

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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