NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Pancreatic Adenocarcinoma

Version 1.2013

NCCN.org
NCCN Guidelines Version 1.2013
Pancreatic Adenocarcinoma

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NCCN Guidelines Panel Disclosures

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NCCN Pancreatic Adenocarcinoma Panel Members

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Introduction

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American Joint Committee on Cancer (AJCC) TNM Staging of Pancreatic Cancer (2010) (ST-1)

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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Updates in Version 1.2013 of the NCCN Guidelines from Version 2.2012 include:

INTRO

• This page is new to the guidelines: “Decisions about diagnostic management and resectability should involve multidisciplinary consultation at a high-volume center with reference to appropriate imaging studies.”

PANC-1

• Changed “Chest CT” to “Chest imaging” throughout the guidelines.
• Added a new footnote: “EUS with FNA if clinically indicated.”

PANC-2

• Modified footnote “c”: “Elevated CA19-9 does not necessarily indicate cancer or advanced disease. CA19-9 may be elevated as a result of biliary obstruction, benign or malignant. In addition, CA19-9 may be undetectable in Lewis antigen-negative individuals.”
• Following the pathway for jaundice, no symptoms of cholangitis and fever added; “Preoperative CA-19-9 (category 3).”
• Borderline resectable, added footnote “d” See Principles of Diagnosis and Staging. Also added a link to PANC-5.

PANC-3

• Following biopsy confirmation of adenocarcinoma, if not performed previously added; “No jaundice, if appropriate, consider duodenal bypass (category 2B for prophylactic duodenal bypass) ± open ethanol celiac plexus block (category 2B).”
• Modified footnote “g”: In selected patients who appear technically resectable but have poor prognostic features, consider neoadjuvant therapy (on clinical trial preferred), which requires biopsy confirmation of adenocarcinoma. For patients with biliary obstruction, durable biliary decompression is required.”

PANC-4

• 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 at a high-volume center. Removed “in the setting of borderline resectable disease.

PANC-5

• Planned neoadjuvant therapy, removed “category 2B.”
• Under the work-up section:
  ➤ Added “Consider” staging laparoscopy and removed “category 2B.”
  ➤ Changed “EUS-directed biopsy” to EUS with FNA.”
  ➤ Changed “Placement of temporary stent” to “Placement of stent (preferably a short metal stent) if biliary ductal obstruction is present.”
• Following neoadjuvant therapy: deleted “Repeat” above abdominal (pancreas protocol), pelvic, and chest imaging.
• Removed category 2B from laparoscopy.

PANC-6

• Following baseline pretreatment, designated pathways for “No prior neoadjuvant therapy” and “Prior neoadjuvant therapy.”
• No prior neoadjuvant therapy, added “or continuous infusion 5-FU” with or without chemoradiation as an adjuvant treatment option.
• Prior neoadjuvant therapy, added “Consider additional chemotherapy.”

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Updates in Version 1.2013 of the NCCN Guidelines from Version 2.2012 include:

- **Modified footnote “m”**: Patients who have received neoadjuvant chemoradiation or chemotherapy may be candidates for additional chemotherapy following surgery “and multidisciplinary review.” 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.

  **PANC-A**

- Modified bullet #1: “Decisions about diagnostic management and resectability should involve multidisciplinary consultation at high-volume center with reference to appropriate high-quality 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. Modified bullet #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 or less) through the abdomen. Multiplanar reconstruction is preferred. 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.

- **PANC-B**

  - Modified the criteria defining resectability status:
    - Tumors considered localized and clearly resectable should demonstrate the following:
      - No radiographic evidence of superior mesenteric vein (SMV) or portal vein (PV) distortion.
    - Tumors considered borderline resectable include the following:
      - Venous involvement of the SMV or PV with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and replacement.

- **PANC-C**

  - Modified bullet: “Consider palliative radiation with or without chemotherapy if not already given as part of primary therapy.”

- **PANC-D**

  - Added a bullet: “Nutritional evaluation when appropriate.”

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Updates in Version 1.2013 of the NCCN Guidelines from Version 2.2012 include:

**PANC-F**

- Table 1: changed “Constraint” to “Recommendation.”
- Page 1: last sentence “Ideally, surgical resection should be attempted 4-8 weeks following CRT.” Changed 6-8 weeks to 4-8 weeks.
- Page 2: Unresectable/locally advanced (non-metastatic): removed “2-4 cycles.” Page 2: Options include: RT 45-54 Gy in 1.8-2.5 fraction, added “Doses higher than 54 Gy may be considered if clinically appropriate.”
- Added (hepaticojejunostomy and gastrojejunostomy may be omitted if clinically appropriate) following “anastamoses” on pages 2, 3, and 4.
- Page 2: RT alone to the primary tumor plus a margin (Typically 25-36 Gy in 2.4-5 Gy fractions) is reasonable for patients with metastatic disease who require local palliation for obstruction or pain. Changed “Typically 30-36 Gy in 2.4-3.0 Gy fractions” to “25-36 Gy in 2.4-5 Gy fractions.”

**PANC-G**

- Acceptable chemotherapy combinations for patients with metastatic disease and good performance status, added:
  - Gemcitabine + nab-paclitaxel changed from (category 2B) to (category 1).
  - A footnote to gemcitabine + erlotinib, “Although this combination significantly improved survival, the actual benefit was small, suggesting that only a subset of patients benefit.”
- Acceptable monotherapy options for patients with metastatic disease and poor performance status, added:
  - Or continuous infusion 5-FU.
- Under neoadjuvant: modified “Although there is insufficient evidence to recommend specific neoadjuvant regimens, most published neoadjuvant regimens incorporate chemoradiation although chemotherapy alone is currently being evaluated.”
- Updated references:

**Discussion**

- The discussion and reference sections have been updated based on the changes in the algorithm.
Decisions about diagnostic management and resectability should involve multidisciplinary consultation at a high-volume center with reference to appropriate imaging studies.

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**Clinical Presentation**

- Clinical suspicion of pancreatic cancer or evidence of dilated pancreatic and/or bile duct (stricture)

**Workup**

- Pancreatic protocol CT or MRI (See PANC-A)
  - No mass in pancreas on imaging
    - Metastatic disease
      - Biopsy confirmation of metastatic site
        - See Metastatic Disease (PANC-9)
      - No metastatic disease
        - No mass in pancreas on imaging
          - Metastatic disease
            - Biopsy confirmation of metastatic site
              - See Metastatic Disease (PANC-9)
          - No metastatic disease
            - Multidisciplinary review
              - Consider endoscopic ultrasonography (EUS)
                - Liver function tests
                  - Chest imaging
                    - Surgical candidate
                      - See PANC-2

- Mass in pancreas on imaging
  - Metastatic disease
    - Biopsy confirmation of metastatic site
      - See Metastatic Disease (PANC-9)
  - No metastatic disease
    - Multidisciplinary review
      - Consider endoscopic ultrasonography (EUS)
        - Liver function tests
          - Chest imaging

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\( ^a \) Multidisciplinary review should ideally involve expertise from surgery, diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, surgery, and pathology.

\( ^b \) EUS with FNA if clinically indicated.
Elevated CA19-9 does not necessarily indicate cancer or advanced disease. CA19-9 may be elevated as a result of biliary obstruction, benign or malignant. In addition, CA19-9 may be undetectable in Lewis antigen-negative individuals. (See Discussion)

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

See Criteria Defining Resectability Status (PANC-B).

See Principles of Surgical Technique (PANC-C) and Pathological Analysis: Specimen Orientation, Histological Sections, and Reporting (PANC-D)

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RESECTABLE WORKUP TREATMENT

Resectable, in high-risk patients or as clinically indicated → Laparotomy

Consider staging laparoscopy if not performed previously

Biopsy confirmation of adenocarcinoma, if not performed previously

Surgical resection → See Adjuvant Treatment and Surveillance (PANC-6)

Unresectable at surgery → Unresectable

No jaundice → If appropriate, consider duodenal bypass (category 2B for prophylactic duodenal bypass) ± open ethanol celiac plexus block (category 2B)

Jaundice → See Locally Advanced Unresectable (PANC-7)

If appropriate, consider duodenal bypass ± open ethanol celiac plexus block (category 2B)

Stenting or biliary bypass ± duodenal bypass (category 2B for prophylactic duodenal bypass) ± open ethanol celiac plexus block when indicated by pain

See Metastatic Disease (PANC-9)

See Principles of Surgical Technique (PANC-C) Pathological Analysis: Specimen Orientation, Histological Sections, and Reporting (PANC-D).

In selected patients who appear technically resectable but have poor prognostic features, consider neoadjuvant therapy (clinical trial preferred), which requires biopsy confirmation of adenocarcinoma. For patients with biliary obstruction, durable biliary decompression is required.

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 at a high-volume center. Performing surgery with a high likelihood of a positive margin is not recommended.

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See Criteria Defining Resectability Status (PANC-B).
See Principles of Diagnosis and Staging #6 (PANC-A).
See Principles of Palliation and Supportive Care (PANC-E).
BORDERLINE RESECTABLE NO METASTASES, PLANNED NEOADJUVANT THERAPY

WORKUP

Planned neoadjuvant therapy

- Biopsy, EUS with FNA preferred
- Consider staging laparoscopy
- Placement of stent (preferably a short metal stent) if biliary ductal obstruction is present

Biopsy positive → Neoadjuvant therapy

Surgical resection

Unresectable at surgery

Jaundice

Disease progression precluding surgery

Stenting or biliary bypass ± duodenal bypass (category 2B for prophylactic duodenal bypass) ± open ethanol celiac plexus block (category 2B)

Biopsy positive → Neoadjuvant therapy (follow pathway above)

Cancer not confirmed → Repeat biopsy

Cancer not confirmed (exclude autoimmune pancreatitis [AIP])

See Planned Resection (PANC-5)

TREATMENT

- See Adjuvant Treatment and Surveillance (PANC-6)
- See Locally Advanced Unresectable (PANC-7)
- See Metastatic Disease (PANC-9)

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BORDERLINE RESECTABLE\textsuperscript{d,e} NO METASTASES, PLANNED RESECTION

WORKUP

Planned Resection\textsuperscript{f} \rightarrow Laparotomy

Laparotomy \rightarrow Surgical resection\textsuperscript{f}

Unresectable at surgery\textsuperscript{f,j} \rightarrow Biopsy confirmation of adenocarcinoma, if not performed previously

If appropriate, consider duodenal bypass (category 2B for prophylactic duodenal bypass) ± open ethanol celiac plexus block (category 2B)

Stenting or biliary bypass ± duodenal bypass (category 2B for prophylactic duodenal bypass) ± open ethanol celiac plexus block when indicated by pain

No jaundice \rightarrow

Jaundice

See Adjuvant Treatment and Surveillance (PANC-6)

See Locally Advanced Unresectable (PANC-7)

See Metastatic Disease (PANC-9)

\textsuperscript{d} See Principles of Diagnosis and Staging (PANC-A).

\textsuperscript{e} See Criteria Defining Resectability Status (PANC-B).

\textsuperscript{f} See Principles of Surgical Technique (PANC-C) and Pathological Analysis: Specimen Orientation, Histological Sections, and Reporting (PANC-D).

\textsuperscript{j} See Principles of Palliation and Supportive Care (PANC-E).

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### Surveillance

- Surveillance every 3-6 mo for 2 years, then annually:
  - H&P for symptom assessment
  - CA 19-9 level (category 2B)
  - CT scan (category 2B)

### Recurrence After Resection

- See PANC-10

### Post-Operative Adjuvant Treatment

- Clinical trial preferred or Systemic gemcitabine or 5-FU/leucovorin or continuous infusion 5-FU before or after chemoradiation (fluoropyrimidine-or gemcitabine-based) or Chemotherapy alone:
  - Gemcitabine (category 1)
  - 5-FU/leucovorin (category 1)
  - Continuous infusion 5-FU
  - Capecitabine (category 2B)

#### No prior neoadjuvant therapy

- No evidence of recurrence or metastatic disease
- Surveillance every 3-6 mo for 2 years, then annually:
  - H&P for symptom assessment
  - CA 19-9 level (category 2B)
  - CT scan (category 2B)

#### No prior neoadjuvant therapy

- Prior neoadjuvant therapy
- No evidence of recurrence or metastatic disease
- Consider additional chemotherapy

#### Prior neoadjuvant therapy

- No evidence of recurrence or metastatic disease
- No evidence of recurrence or metastatic disease
- Surveillance every 3-6 mo for 2 years, then annually:
  - H&P for symptom assessment
  - CA 19-9 level (category 2B)
  - CT scan (category 2B)

### Note:

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

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1 See Principles of Radiation Therapy (PANC-F).

m Patients who have received neoadjuvant chemoradiation or chemotherapy may be candidates for additional chemotherapy following surgery and multidisciplinary review. 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.
LOCALLY ADVANCED UNRESECTABLE

WORKUP

Adenocarcinoma confirmed

If jaundice: placement of stent (expandable metal stent preferred)

Good performance status

See Treatment (PANC-8)

Locally advanced unresectable

Biopsy if not previously done

Cancer not confirmed

If jaundice: placement of stent (preferably a short metal stent) with brushings

Repeat biopsy

Cancer not confirmed

Repeat biopsy

Other cancer confirmed

Treat with appropriate NCCN Guideline

Other cancer confirmed

Treat with appropriate NCCN Guideline

Note: All recommendations are category 2A unless otherwise indicated.

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n Unless biliary bypass performed at time of laparoscopy or laparotomy.

EUS-guided FNA ± core biopsy at a center with multidisciplinary expertise is preferred.

Defined as ECOG 0-1 with good pain management, patent biliary stent, and adequate nutritional intake.
<table>
<thead>
<tr>
<th>Locally Advanced Unresectable</th>
<th>Treatment</th>
<th>Salvage Therapy</th>
</tr>
</thead>
</table>
| **Good Performance Status**   | Chemotherapy:  
                    • Clinical trial preferred or  
                    • FOLFIRINOX or  
                    • Gemcitabine or  
                    • Gemcitabine-based combination therapy or  
                    • Capecitabine or continuous infusion 5-FU (category 2B)  
                    Chemoradiation in selected patients (locally advanced without systemic metastases), preferably following an adequate course of chemotherapy | Clinical trial (preferred) or  
Fluoropyrimidine-based chemotherapy if previously treated with gemcitabine-based therapy or  
Gemcitabine-based therapy if previously treated with fluoropyrimidine-based therapy or  
Chemoradiation if not previously given and if primary site is the sole site of progression |

**Poor Performance Status**  
Gemcitabine (category 1) or  
Best supportive care  

**Best Supportive Care**  
Laparoscopy as indicated to evaluate distant disease.  
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.  
Best reserved for patients who maintain a good performance status.

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**See Principles of Palliation and Supportive Care (PANC-E).**  
**See Principles of Radiation Therapy (PANC-F).**  
**Defined as ECOG 0-1 with good pain management, patent biliary stent, and adequate nutritional intake.**  
**See Principles of Chemotherapy (PANC-G).**
## NCCN Guidelines Version 1.2013
### Pancreatic Adenocarcinoma

### NCCN Guidelines Index

## Pancreatic Table of Contents

### Discussion

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**Pancreatic Adenocarcinoma**

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### METASTATIC DISEASE

#### TREATMENT

- **Good performance status**
  - Clinical trial preferred
  - or
  - FOLFIRINOX\(^q\) (category 1)
  - or
  - Gemcitabine + nab-paclitaxel\(^q\) (category 1)
  - or
  - Gemcitabine + erlotinib\(^q\) (category 1)
  - or
  - Gemcitabine-based combination therapy\(^q\)
  - or
  - Gemcitabine\(^q\) (category 1)
  - or
  - Capecitabine\(^q\) or continuous infusion 5-FU\(^q\) (category 2B)

#### SALVAGE THERAPY\(^u\)

- Clinical trial (preferred)
- or
- Fluoropyrimidine-based chemotherapy if previously treated with gemcitabine-based therapy\(^q\)
- or
- Gemcitabine-based therapy if previously treated with fluoropyrimidine-based therapy\(^q\)
- or
- RT for severe pain refractory to narcotic therapy\(^l\)

#### Poor performance status

- Gemcitabine\(^r\) (category 1)
- or
- Best supportive care\(^i\)

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\(^i\) See Principles of Palliation and Supportive Care (PANC-E).

\(^l\) See Principles of Radiation Therapy (PANC-F).

\(^n\) Unless biliary bypass performed at time of laparoscopy or laparotomy.

\(^p\) Defined as ECOG 0-1 with good pain management, patent biliary stent, and adequate nutritional intake.

\(^q\) See Principles of Chemotherapy (PANC-G).

\(^u\) Best reserved for patients who maintain a good performance status.
**NCCN Guidelines Version 1.2013**

**Pancreatic Adenocarcinoma**

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**Discussion**

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**TREATMENT**

**SALVAGE THERAPY**

**RECURRENCE AFTER RESECTION**

- **Local recurrence**
  - Consider biopsy for confirmation (category 2B)
  - Clinical trial (preferred)
  - or
  - Consider chemoradiation if not previously done
  - or
  - Alternative systemic chemotherapy
  - or
  - Best supportive care

- **Metastatic disease with or without local recurrence**
  - Greater than 6 mo from completion of primary therapy
    - Clinical trial (preferred)
    - or
    - Systemic therapy as previously administered
    - or
    - Alternative systemic chemotherapy
    - or
    - Best supportive care
  - Less than 6 mo from completion of primary therapy
    - Clinical trial (preferred)
    - or
    - Switch to alternative systemic chemotherapy
    - or
    - Best supportive care

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**See Principles of Palliation and Supportive Care (PANC-E).**

**See Principles of Radiation Therapy (PANC-F).**

**See Principles of Chemotherapy (PANC-G).**

**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 at high-volume center with reference to appropriate high-quality 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 (3 mm or less) through the abdomen. Multiplanar reconstruction is preferred. 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 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 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 clearly resectable should demonstrate the following:
- No distant metastases
- No radiographic evidence of superior mesenteric vein (SMV) or portal vein (PV) distortion.
- 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 or PV with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and replacement.
- 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.

Tumors considered to be unresectable demonstrate the following:
- HEAD
  - Distant metastases
  - Greater than 180 degrees SMA encasement, any celiac abutment, IVC
  - 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.


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

Pancreatoduodenectomy (Whipple technique)
The goals of surgical extirpation of pancreatic carcinoma focus on the achievement of an R0 resection, as a margin positive specimen is associated with poor long-term survival.\(^1,2\) Achievement of a margin negative dissection must focus on meticulous perivascular dissection of the lesion in resectional procedures, recognition of the need for vascular resection and/or reconstruction, and the potential need for extrapancreatic organ resection. Of course the biology of the cancer might not allow for an R0 resection even with the most meticulous surgery.

- Medial dissection of pancreatic head lesions is best achieved by complete mobilization of the portal and superior mesenteric veins from the uncinate process (assuming no evidence of tumor infiltration). Skeletalization of the lateral, posterior and anterior borders of the superior mesenteric artery down to the level of the adventitia will maximize uncinate yield and radial margin.\(^3,4\)
- In the absence of frank venous occlusion noted on preoperative imaging, the need for lateral venorrhaphy or complete portal or superior mesenteric vein resection and reconstruction to achieve an R0 resection may be suggested but is often not known until division of the pancreatic neck has occurred. Tethering of the carcinoma to the lateral wall of the portal vein is not uncommon and requires careful dissection to free the vein from the pancreatic head if in fact it is possible to do so. Differentiation of tumor infiltration into the vein wall from tumor related desmoplasia is frequently impossible to ascertain. Data support an aggressive approach to partial or complete vein excision if tumor infiltration is suspected, although acceptance of this concept (particularly with respect to vein resection) is not universal.
- While further data with respect to arterial resection are clearly needed, judicious utilization of this technique would appear to be reasonable in very select populations.

Distal Pancreatectomy
The goals of left-sided resection are similar to those of pancreateoduodenectomy although they are often more difficult to achieve due to the advanced stage at which most of these cancers are discovered.

- An R0 distal pancreatectomy for adenocarcinoma mandates en bloc organ removal beyond that of the spleen alone in up to 40% of patients.\(^5,6\)
- Similar to the Whipple procedure, lateral venorrhaphy, vein excision and reconstruction, and dissection to the level of the celiac axis and SMA adventitia should be performed if complete tumor clearance can be achieved.\(^5,7\)
- Utilization of radical resections is associated with an increase in blood loss, transfusion requirements, operating time, length of stay, and morbidity, mortality remains acceptable.\(^5,7\)
PATHOLOGICAL ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGICAL SECTIONS AND REPORTING

The primary purpose of pathological analysis of the pancreatic specimen is to determine the pathological stage of the tumor by evaluating the type, grade, size and extent of the cancer.

Whipple Specimen

- Specimen orientation
  - Specimen orientation and inking involves both pathologist and surgeon as this will help to ensure accurate assessment of the size and extent of the tumor. There should be either direct communication between the surgeon and pathologist for proper orientation and margin identification, or the surgeon should identify the important margins with a clearly understood and documented method [e.g. written on the pathology requisition]; for example: stitch on posterior margin, safety pin on the retroperitoneal/uncinate margin.

- Margins
  - Definitions of the margins and uniformity of nomenclature are critical to accurate reporting
    - SMA (Retroperitoneal/uncinate) Margin: The most important margin is the soft tissue directly adjacent to the proximal 3-4 cm of the superior mesenteric artery. This margin is often referred to as the “retroperitoneal margin” or “posterior margin”, but has also been referred to as the “uncinate margin” or “mesenteric margin”. More recently, this margin has been referred to as the “SMA margin” to correlate with its location on the specimen. Radial rather than en face sections of this margin will more clearly demonstrate how closely this margin is approached by tumor. The simple step of palpating the specimen can help guide the pathologist as to the best spot along the SMA margin to select for sampling.
    - Posterior Margin: This margin is from the posterior caudad aspect of the pancreatic head that merges with the uncinate margin and that appears to be covered by loose connective tissue. Radial rather than en face sections of this margin will more clearly demonstrate whether it is involved by tumor. In some instances this margin can be included in the same section as the SMA margin section.
    - Portal Vein Groove Margin: This is the smooth-surfaced groove on the posterior-medial surface of the pancreatic head that rests over the portal vein. Radial rather than en face sections of this margin will more clearly demonstrate whether it is involved by tumor and also will provide the distance from the tumor from the margin. As is true for the posterior margin, in some instances this margin can be included in the same section as the SMA margin section.
    - Portal Vein Margins: If an en bloc partial or complete vein resection is added to the surgical specimen it should be marked separately. En face proximal and distal end margins of the vein should be separately submitted as Proximal Portal Vein Margin and Distal Portal Vein Margin. A section documenting tumor invasion into the vein wall should also be submitted. If feasible, this section should be a full thickness of the vein wall demonstrating the depth of tumor invasion as this has been shown to have prognostic value.³⁸
    - Pancreatic Neck (transection) Margin: This is the en face section of the transected pancreatic neck. The section should be placed into the cassette with true margin facing up so that the initial section into the block represents the true surgical margin.
    - Bile Duct Margin: This is the en face section of the bile duct end. The section should be removed from the unopened duct and placed into the cassette with true margin facing up so that the initial section into the block represents the true surgical margin.

- Other margins analyzed in Whipple specimens include the proximal and distal enteric margins (en face sections) and anterior surface (closest representative). The anterior surface is not a true margin, but identification and reporting of this surface when positive may portend a risk of local recurrence, and so should be reported in all cases.⁹⁺¹²

- Collectively, these pancreatic tissue surfaces constitute the circumferential transection margin. Designating the various specific margins with different colored inks will allow recognition on microscopy.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PATHOLOGICAL ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGICAL SECTIONS AND REPORTING

- Histological sectioning
  - The approach to histological sectioning is determined by the unique characteristics of the tumor, but is also influenced by institutional preferences, expertise and experience. Options include axial, bi- or multi-valve slicing and perpendicular sliding. Some experts in the field bisect the pancreas along probes placed in the bile and pancreatic ducts and then serially section along each half of the pancreas.
  - Axial slicing provides an overall assessment of the epicenter of the tumor relative to the ampulla, bile duct, duodenum and pancreas, and all of the pancreatic circumferential tissue margins mentioned above.
  - There is no one correct way to dissect a Whipple specimen. The most important aspects of dissection are clear and accurate assessment of the margins.
  - It is currently unknown what constitutes an adequate margin in pancreatic carcinoma resection specimens. A standardized definition of this would allow better stratification of patients into adjuvant regimens following surgical extirpation. For instance, if less than 1mm clearance is associated with an unacceptably high incidence of local recurrence then strong consideration for post-operative radiation therapy might be indicated if not received pre-operatively. Tumor clearance should be reported in millimeters for the SMA margin described above to allow prospective accumulation of this important data for future analysis.
  - Attached organs resected with the specimen en bloc require serial sectioning to assess not only direct extension, but metastatic deposits as well. One section that demonstrates direct invasion of the organ and/or a separate metastatic deposit is required.

Distal Pancreatectomy
- In left sided resections the peripancreatic soft tissue margins and the pancreatic neck are assessed. Additionally, involvement of the splenic vessels should be documented and invasion of the spleen is important to determine, as direct tumor invasion constitutes a pT4 pathological stage.
- Frozen section analysis of the pancreatic neck is recommended.
- Margins definitions are as follows:
  - Proximal pancreatic (transection) margin: A full en face section of the pancreatic body along the plane of transection. The section should be placed into the cassette with true margin facing up so that the initial section into the block represents the true surgical margin. More than one block may be needed.
  - Anterior (cephalad) peripancreatic (peripheral) surface: This surface demonstrates the relationship between the tumor and the anterior or cephalad peripancreatic soft tissue and can be representative if grossly positive. Several such sections should be taken closest to the tumor to document absence of involvement; the exact number is dependent on the degree of ambiguity of involvement grossly.
  - Posterior (caudal) peripancreatic (peripheral) margin: This margin demonstrates the relationship between the tumor and the posterior or caudal peripancreatic soft tissue and can be representative if grossly positive. Several such sections should be taken closest to the tumor to document absence of involvement; the exact number is dependent on the degree of ambiguity of involvement grossly.
PATHOLOGICAL ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGICAL SECTIONS AND REPORTING

Reporting

The NCCN Pancreatic Cancer Panel currently supports pathology synoptic reports from the College of American Pathologists (CAP). The proposal included herein is an abbreviated minimum analysis of pancreatic cancer specimens from the CAP recommendations. In addition to the standard TNM staging, other variables are included all of which have prognostic implications in the evolution of this disease.\textsuperscript{13,14}

Specimen type

- Tumor size (obtained from careful gross measurement of the largest dimension of the tumor in cm).
- Histologic grade (G (x-4))
- Primary tumor extent of invasion (T (x-4))
- Regional lymph nodes (N (x-1))
  - # Nodes recovered
  - # Nodes involved
- Metastases (M (0-1))
- Margins: [Involvement should be defined and surgical clearance measured in mm]
  - Whipple Resection:
    - SMA (Retropertitoneal/uncinate) Margin
    - Posterior Margin
    - Portal Vein Groove Margin
    - Pancreatic Neck (transection) Margin
      - Bile Duct Margin
    - Enteric Margins
    - Anterior surface
  - Distal pancreatectomy:
    - Proximal pancreatic (transection) margin
    - Anterior (cephalad) peripancreatic (peripheral) surface
    - Posterior (caudal) peripancreatic (peripheral) margin
- Lymphatic (small vessel) invasion (L)
- Vascular (large vessel) invasion (V)
- Perineural invasion (P)
- Additional pathologic findings
  - Pancreatic intraepithelial neoplasia
  - Chronic pancreatitis

Final Stage: G, T, N, M, L, V, P

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Continued on next page

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PRINCIPLES OF PALLIATION AND SUPPORTIVE CARE

Objectives: Prevent and ameliorate suffering, while ensuring optimal quality of life

- **Biliary obstruction**
  - Endoscopic biliary stent (preferred method)
  - Percutaneous biliary drainage with subsequent internalization
  - Open biliary-enteric bypass

- **Gastric outlet obstruction**
  - Good performance status
    - Gastrojejunostomy (open or laparoscopic) ± J-tube
    - Consider enteral stent  
  - Poor performance status
    - Enteral stent
    - Percutaneous endoscopic gastrostomy (PEG) tube

- **Severe tumor-associated abdominal pain**
  - EUS-guided celiac plexus neurolysis (fluoroscopic- or CT-guided if unavailable)
  - Consider palliative radiation with or without chemotherapy 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)
  - Nutritional evaluation when appropriate.

- **Pancreatic insufficiency (inadequate production of digestive enzymes)**
  - Pancreatic enzyme replacement

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

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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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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 fluoropyrimidine (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
- Ideally, surgical resection should be attempted 4-8 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):

- Induction chemotherapy followed by 5-FU or gemcitabine-based CRT.\textsuperscript{7,8}
- Upfront fluoropyrimidine (CI 5-FU or capecitabine)-based chemoradiation (CRT) in select patients.
- Upfront gemcitabine-based CRT in select patients.\textsuperscript{9,10}

Options include:

- RT 45-54 Gy in 1.8-2.5 Gy fractions (doses higher than 54 Gy may be considered if clinically appropriate) or
- 36 Gy in 2.4 Gy fractions.\textsuperscript{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.\textsuperscript{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.\textsuperscript{13}
  - Gemcitabine or CI 5-FU (1 cycle) followed by CI 5-FU/RT followed by maintenance gemcitabine or CI 5-FU.\textsuperscript{14}
  - Gemcitabine or bolus 5-FU/leucovorin\textsuperscript{15}
  - Gemcitabine or bolus 5-FU/leucovorin for 2-6 cycles followed by fluoropyrimidine- (CI 5-FU or capecitabine) based CRT.\textsuperscript{16}

RT 45-46 Gy in 1.8-2 Gy fractions to the tumor bed, surgical anastomoses (hepaticojejunostomy and gastrojejunostomy may be omitted if clinically appropriate), and adjacent lymph node, followed by an additional 5-9 Gy to the tumor bed and anastomoses.\textsuperscript{17}

Palliative:

- See Principles of Palliation and Supportive Care (PANC-E).
  - RT alone to the primary tumor plus a margin (Typically 25-36 Gy in 2.4-5 Gy fractions) is reasonable for patients with metastatic disease who require local palliation for obstruction or pain.\textsuperscript{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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Continued on next page
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 (hepaticojejunostomy and gastrojejunostomy may be omitted if clinically appropriate), 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 Recommendations [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 (hepaticojejunostomy and gastrojejunostomy may be omitted if clinically appropriate), 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. 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 Recommendations

<table>
<thead>
<tr>
<th>Structure</th>
<th>Unresectable/Preoperative Recommendations</th>
<th>Adjuvant/Resected Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney (right and left)</td>
<td>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.</td>
<td>If two functioning kidneys present, not more than 50% of the right and 65% of the left kidney should receive &gt;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.</td>
</tr>
<tr>
<td>Stomach, duodenum, jejunum</td>
<td>Max dose ≤55 Gy; not more than 30% of the volume can be between 45 and 55 Gy.</td>
<td>Max dose ≤55 Gy; &lt;10% of each organ volume can receive between 50-53.99 Gy. &lt;15% of each organ volume can receive 45-49.99 Gy.</td>
</tr>
<tr>
<td>Liver</td>
<td>Mean dose cannot exceed 30 Gy.</td>
<td>Mean liver dose ≤25 Gy.</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Max dose to a volume of at least 0.03 cc must be ≤45 Gy.</td>
<td>Max dose ≤45 Gy.</td>
</tr>
</tbody>
</table>

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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### PRINCIPLES OF RADIATION THERAPY

#### Table 2. Commonly used radiation therapy abbreviations

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

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


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 chemotherapy combinations for patients with good performance status include:
  - FOLFIRINOX\(^1\) (category 1)
  - Gemcitabine + nab-paclitaxel\(^2\) (category 1)
  - Gemcitabine + erlotinib\(^3\) (category 1)\(^a\)
  - Gemcitabine + capecitabine\(^4\)
  - Gemcitabine + cisplatin\(^5\) (especially for patients with possible hereditary cancers)
  - Fixed-dose rate gemcitabine, docetaxel, capecitabine (GTX regimen)\(^6\) (category 2B)
  - Fluoropyrimidine + oxaliplatin (category 2B) (e.g., 5-FU/leucovorin/oxaliplatin\(^7\) or CapeOx\(^8\))

- Acceptable monotherapy options for patients with poor performance status 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 or continuous infusion 5-FU (category 2B)

- 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.

\(^a\)Although this combination significantly improved survival, the actual benefit was small, suggesting that only a subset of patients benefit.
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.  
- 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.
- 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.
- 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 or CapeOx) for patients previously treated with gemcitabine-based therapy.

Neoadjuvant

- Although there is insufficient evidence to recommend specific neoadjuvant regimens, most published neoadjuvant regimens incorporate chemoradiation although chemotherapy alone is currently being evaluated.
PRINCIPLES OF CHEMOTHERAPY (3 of 3)

References


# 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)

### 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

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*This also includes the “PanInIII” classification.

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NCCN Guidelines Version 1.2013
Pancreatic Adenocarcinoma

Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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Overview

During the year 2013 in the United States, an estimated 45,220 people will be diagnosed with pancreatic cancer, and approximately 38,460 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 have a higher incidence of pancreatic cancer than white Americans.²,³ Furthermore, the incidence of pancreatic cancer in the United States increased from 1999 to 2008, possibly because of the increasing prevalence of obesity and other unknown factors.³ Mortality rates have remained largely unchanged.⁴

In these NCCN Guidelines for Pancreatic Adenocarcinoma, the diagnosis and management of adenocarcinomas of the exocrine pancreas are discussed; neuroendocrine tumors are not included (please see the NCCN Guidelines for Neuroendocrine Tumors, available at www.NCCN.org). These NCCN Guidelines are intended to assist with clinical decision-making, but they cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the panel members during the process of developing and updating 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. A recent study of 3706 patients treated for pancreatic cancer in large California hospitals showed that compliance with these NCCN Guidelines for Pancreatic Adenocarcinoma, defined very permissively, improves survival.⁵

As an overall guiding principle of these guidelines, the panel believes that decisions about diagnostic management and resectability of pancreatic cancer should involve multidisciplinary consultation at high-volume centers with reference to appropriate imaging studies. In addition, the panel believes that increasing participation in clinical trials (currently only 4.5% of patients enroll on a pancreatic cancer trial⁶) is critical to making progress in this disease. Thus, 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.⁷-¹² There is also some evidence that increased consumption of red/processed meat and dairy products is associated with an elevation in pancreatic cancer risk,¹³,¹⁴ although other studies have failed to identify dietary risk factors for the disease.¹¹,¹⁵ Occupational exposure to chemicals such as beta-naphthylamine and benzidine is associated with increased risk for pancreatic cancer,¹⁶ as is heavy alcohol consumption.⁷,⁹,¹⁷ Recent data also suggest that low plasma 25-hydroxyvitamin D levels may increase the risk of pancreatic cancer.¹⁸ Chronic pancreatitis has also been identified as a risk factor for pancreatic cancer,¹⁹,²⁰ and a more recent study demonstrated a 7.2-fold increased risk of pancreatic cancer for patients with a history of pancreatitis.²¹ An increased body mass index (BMI) is also associated with an increased risk for pancreatic cancer.²²-²⁴ Overall, 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.

The association between diabetes mellitus and pancreatic cancer is particularly complicated. Numerous studies have shown an association...
between new-onset non-insulin-dependent diabetes and the development of pancreatic cancer,\(^25\)\(^{27}\) especially in those who are elderly, have a lower BMI, experience weight loss, or do not have a family history of diabetes.\(^28\) Some studies also showed an association of pancreatic cancer with diabetes of longer duration, but not with a >8 year history of diabetes.\(^29\)\(^30\) However, certain risk factors such as obesity, associated with both diabetes and pancreatic cancer, may confound these analyses.\(^31\) Furthermore, the use of diabetic medications has been reported to alter pancreatic cancer risk. The use of insulin or sulfonylureas has been found to be associated with an increased risk for pancreatic cancer.\(^32\)\(^{34}\) On the other hand, metformin may be associated with a reduced risk for pancreatic and other cancers.\(^32\)\(^{35}\) In addition, metformin use has been reported to result in higher pancreatic cancer survival in diabetics. A retrospective analysis of 302 patients with pancreatic cancer and diabetes treated at The University of Texas MD Anderson Cancer Center found that metformin use was associated with increased survival at 2 years (30.1% vs. 15.4%; \(P = .004\)) and increased overall survival (OS) (15.2 months vs. 11.1; \(P = .009\)).\(^36\) The OS difference was significant only in patients without distant metastases and remained significant when insulin users were excluded.

True familial pancreatic cancer is rare; however, a genetic predisposition may be present in up to 5% to 10% of patients,\(^37\)\(^{39}\) and familial excess of pancreatic cancer is associated with high risk.\(^11\)\(^39\) A germline mutation in the \(CDKN2A\) (p16) gene has been reported in families with pancreatic cancer and melanoma.\(^40\)\(^{43}\) An excess of pancreatic cancer is also seen in families harboring \(BRCA2\) (breast cancer susceptibility gene-2) mutations,\(^44\)\(^{46}\) and particular mutations in the \(PALB2\) and \(MSH2\) genes have recently been identified as possibly increasing pancreatic cancer susceptibility. Recently, whole-genome sequencing allowed for the identification of germline mutations in \(ATM\) in 2 kindreds with familial pancreatic cancer.\(^49\) Further analyses then revealed \(ATM\) mutations in 4 of 166 individuals with familial pancreatic cancer.

In addition, pancreatic cancer is associated with 2 cancer syndromes. Germline mutations in the \(STK11\) gene result in Peutz-Jeghers syndrome, in which individuals have gastrointestinal polyps and an elevated risk for colorectal cancer.\(^50\)\(^{52}\) These individuals also have a highly elevated risk for developing pancreatic cancer.\(^53\)\(^54\) Lynch syndrome is the most common form of genetically determined colon cancer predisposition and is caused by germline mutations in DNA mismatch repair (MMR) genes (\(MLH1\), \(MSH2\), \(MSH6\), or \(PMS2\)).\(^55\)\(^{59}\) Patients with Lynch syndrome also have an elevated risk for pancreatic cancer.\(^60\)

**Pancreatic Cancer Screening**

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.\(^61\) Preinvasive pancreatic neoplasms were detected in 10% of high-risk patients, suggesting that EUS may have a promising role in screening high-risk patients. The CAPS Consortium recently reported results of their CAPS3 study, in which 225 asymptomatic high-risk individuals were independently (in a blinded manner) screened once with CT, MRI, and EUS.\(^62\) In this study, 42% of individuals were found to have an abnormality; 5 individuals underwent surgical interventions, 3 of whom had high-grade dysplasia in small intraductal papillary mucinous neoplasms and intraepithelial neoplasias. When results of the 3 screening modalities were compared, EUS detected
abnormalities in 42% of individuals, versus 33% and 11% for MRI and CT, respectively.

Interestingly, results from a prospective cohort study that followed high-risk individuals for an average of 4.2 years with annual MRI were recently published. Although 32% of participants were found to have pancreatic abnormalities and some intraductal papillary mucinous neoplasms and intraepithelial neoplasias were resected, 3 patients developed pancreatic adenocarcinoma (2 metastatic, 1 recurrent 30 months post-resection) despite screening. These results could be due to inadequate imaging or from rapid malignant progression. The diagnostic yield of pancreatic cancer screening with EUS or MRI in asymptomatic individuals at high risk for familial disease has also been investigated in other studies. Although results from these trials seem promising overall, the malignant potential of some preinvasive pancreatic lesions and the impact of screening on survival are presently unclear.

An international CAPS Consortium summit with 49 multidisciplinary experts was held to develop consensus guidelines for pancreatic cancer screening. The group recommends screening with EUS and/or MRI/magnetic resonance cholangiopancreatography (MRCP) for high-risk individuals, defined as first-degree relatives of patients with pancreatic cancer from familial kindreds; carriers of p16 or BRCA2 mutations with an affected first-degree relative; patients with Peutz-Jeghers syndrome; and patients with Lynch syndrome and an affected first-degree relative. The group also concluded that more evidence is needed regarding optimal management of patients with detected lesions, the age to begin screening, and screening intervals.

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. Thus, pancreatic carcinoma should be considered in diabetic patients with unusual manifestations, such as abdominal symptoms and continuous weight loss.

All patients for whom there is clinical suspicion of pancreatic cancer or evidence of a dilated duct (stricture) should undergo initial evaluation by CT or MRI performed according to a defined pancreas protocol. Subsequent decisions regarding diagnostic management and resectability should involve multidisciplinary consultation, with reference to appropriate studies to evaluate the extent of disease. The Panel recommends that a multidisciplinary review ideally involve expertise from surgery, diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, and pathology.

The AJCC has developed staging criteria for adenocarcinoma of the pancreas that follow the tumor/node/metastasis (TNM) system. 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 or MRI to determine resectability status, these staging criteria also include information that can be determined only through postsurgical pathologic evaluation of resected tumor. Recent validation of concordance between AJCC stage and OS has been provided through evaluation of
121,713 patients with pancreatic adenocarcinoma included in the National Cancer Data Base (NCDB).71

For clinical purposes, however, most NCCN Member Institutions use a clinical classification system based mainly on results of presurgical imaging studies. Following staging by CT or MRI (and EUS/endoscopic retrograde cholangiopancreatography [ERCP] in some cases), liver function tests, and chest imaging, disease is classified as: 1) resectable; 2) borderline resectable (ie, tumors that are involved with nearby structures so as to be neither clearly resectable nor clearly unresectable); 3) locally advanced unresectable (ie, tumors that are involved with nearby structures to an extent that renders them unresectable despite the absence of evidence of metastatic disease); or 4) disseminated, and this system is used throughout the guidelines. See Criteria for Resection below for more detailed definitions.

Imaging Evaluations

Pancreatic Protocol CT and MRI
Pancreatic protocol CT is the most widely available and best-validated imaging modality for diagnosing and staging patients with pancreatic cancer.72,77 Studies have shown that 70% to 85% of patients determined by CT imaging to have resectable tumors were able to undergo resection.72,74-78 However, the sensitivity of CT for small hepatic and peritoneal metastases is limited. Pancreas protocol MRI is emerging as an equivalent alternative to CT, and was added to the 2012 guidelines as an option for the initial workup of patients for whom pancreatic cancer is suspected. MRI can also 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.79,80

Unlike many other cancers, imaging is the primary means through which the stage of pancreatic cancer is determined. High-quality multi-phase imaging can help to preoperatively distinguish between patients eligible for resection with curative intent and those with unresectable disease. The criteria for defining resectable disease favor specificity over sensitivity to avoid denying surgery to patients with a potentially resectable tumor.72 Optimal multi-phase imaging technique (CT or MRI) includes a non-contrast phase plus arterial, pancreatic parenchymal, and portal venous phases of contrast enhancement with thin cuts (3 mm or less) 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.72,76,80,81 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. A multi-phasic pancreatic protocol also allows for selective visualization of important arterial (eg, celiac axis, superior mesenteric artery [SMA], peripancreatic arteries) and venous structures (eg, superior mesenteric vein [SMV], splenic vein, portal vein [PV]), thereby providing an assessment of vascular invasion by the tumor. All of this information can improve the prediction of resectability. Software allowing for 3-D reconstruction of imaging data can provide additional valuable information on the anatomic relationship between the pancreatic tumor and the surrounding blood vessels and organs, and multiplanar reconstruction is preferred. However, further development of this technology may be needed before it is routinely integrated into clinical practice.77

Patients commonly present to the oncologist with a non-pancreas protocol CT already performed. The panel feels that if the CT scan is of high quality, it can be sufficient. If not, a pancreas protocol CT or MRI is recommended. Such selective reimaging was shown to change the
staging and management of patients with pancreatic adenocarcinoma in 56% of cases retrospectively reviewed at one institution.\textsuperscript{82}

**Endoscopic Ultrasound**

NCCN Member Institutions vary in the use of additional staging technologies, such as EUS. The role of EUS in staging is felt to be complementary to CT or MRI, providing additional information for patients whose initial scans show no lesion or whose lesions have questionable involvement of blood vessels or lymph nodes.\textsuperscript{68,83} In particular, EUS may provide assessment of certain types of vascular invasion.\textsuperscript{84,85} It is the consensus of the panel that while accuracy of EUS in assessing the involvement of certain veins (eg, PV) is high, this technique is less accurate in imaging tumor invasion of the SMA.\textsuperscript{86}

EUS is also used to discriminate between benign and malignant strictures or stenosis, because severe stenosis and marked proximal dilatation most often indicate malignancy.\textsuperscript{87} 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 they are frequently associated with a dilated main pancreatic duct. Some therapeutic interventions can also be done with EUS (eg, celiac block, removal of ascites). Because this procedure is operator dependent, some divergence in use may occur because of differing technical capabilities and available expertise.

**Endoscopic Retrograde Cholangiopancreatography and MRI/Magnetic Resonance Cholangiopancreatography**

ERCP is a technique that combines endoscopic and fluoroscopic procedures and is generally limited to therapeutic interventions.\textsuperscript{88} In the guidelines, ERCP with duct brushing cytology is recommended for patients without a mass in the pancreas and without evidence of metastatic disease who require biliary decompression and who undergo additional imaging with EUS to help establish a diagnosis.\textsuperscript{89} 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/ MRCP is considered to be equivalent to EUS/ERCP in this setting.

**PET/CT**

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.\textsuperscript{90} 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 or MRI, although it can be considered as an adjunct to a formal pancreatic CT or MRI protocol in high-risk patients.

**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.\textsuperscript{91,92} 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). For example, preoperative serum CA 19-9 levels >100 U/mL (see discussion of Biomarkers, below) have been associated with a greater likelihood of advanced disease and an increased probability of a positive finding on staging laparoscopy. 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. 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 patients with body and tail lesions) is used routinely in some NCCN Member 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 resectable pancreatic cancer considered to be at increased risk for disseminated disease, and as a category 2B recommendation for patients with borderline resectable disease prior to and following administration of neoadjuvant therapy because it is not uniformly done at all NCCN Member Institutions. The panel considers positive cytology from washings obtained at laparoscopy or laparotomy to be equivalent to M1 disease.

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, 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 EUS guidance (preferred) or CT. EUS with FNA is preferable to 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. Additional risks of CT-directed FNA biopsy include the potential for greater bleeding and infection because of the need to traverse vessels and bowel. EUS with FNA also gives the benefit of additional staging information at the time of biopsy.

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. EUS-guided FNA of cystic pancreatic lesions can also be useful in the differential diagnosis of non-neoplastic and neoplastic lesions that are difficult to discriminate with imaging studies. In rare cases when an EUS-directed biopsy cannot be obtained from a borderline resectable or unresectable patient, other acceptable methods of biopsy exist. For instance, intraductal biopsies can be obtained via endoscopic cholangioscopy. A percutaneous approach or a laparoscopic biopsy are other alternatives. Pancreatic ductal brushings or biopsies can also be obtained at the time of ERCP, often revealing malignant cytology consistent with pancreatic adenocarcinoma.
If a biopsy does not confirm malignancy, at least 1 repeat biopsy should be performed; EUS-guided FNA with or without a core biopsy at a center with multidisciplinary expertise is preferred. Alternative diagnoses including autoimmune pancreatitis should be considered (see Differential Diagnoses, below). A positive biopsy is required before administration of chemotherapy. However, it is important to reiterate that biopsy proof of malignancy is not required before surgical resection for clearly resectable or borderline 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.

**Biomarkers**

Many tumor-associated antigens have been studied in connection with pancreatic adenocarcinoma, including carcinoembryonic antigen (CEA), pancreatic anti-oncelfetal antigen, tissue polypeptide antigen, cancer antigen (CA) 125, and carbohydrate antigen (CA) 19-9. The best validated and most clinically useful biomarker is CA 19-9, a sialylated Lewis A blood group antigen. CA 19-9 is commonly expressed and shed in pancreatic and hepatobiliary disease, and 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).\(^{101}\) CA 19-9 has potential uses in diagnosis, in screening, in staging, in determining resectability, as a prognostic marker after resection, and as a predictive marker for response to chemotherapy.\(^{102}\)

CA 19-9 is a good diagnostic marker, with sensitivity of 79% to 81% and specificity of 82% to 90% in symptomatic patients, but its low positive predictive value makes it a poor biomarker for screening.\(^{103}\)

Preoperative CA 19-9 levels correlate with both AJCC staging and resectability and thus can provide additional information for staging and determining resectability, along with information from imaging, laparoscopy, and biopsy.\(^{104-106}\)

CA 19-9 also seems to have value as a prognostic marker. Low postoperative serum CA 19-9 levels or a serial decrease in CA 19-9 levels following surgery have been found to correlate with survival for patients undergoing resection for pancreatic cancer.\(^{103,104,106-112}\) 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 (HR, 3.53; \(P < .0001\)).\(^{108}\)

Furthermore, in a prospective study of patients with advanced pancreatic cancer, pretreatment CA 19-9 serum levels were shown to be an independent prognostic factor for survival.\(^{113}\)

Finally, the change in CA 19-9 levels after chemotherapy in patients with advanced disease has been shown to be a reliable predictive marker for response to treatment.\(^{113-117}\) New data from an analysis of 260 consecutive patients support the predictive role of postoperative CA 19-9 levels.\(^{111}\) Among patients with CA 19-9 levels of <90 U/mL, those who received adjuvant therapy (mostly gemcitabine-based) had a longer disease-free survival than those who did not (26.0 months vs. 16.7 months; \(P = .011\)). In contrast, patients with higher CA 19-9 levels did not appear to benefit from adjuvant therapy, with disease-free survival of 16.2 months and 9.0 months for those receiving or not receiving adjuvant therapy, respectively (\(P = .719\)). In this same study, the 11 patients with post-adjuvant therapy CA 19-9 levels <37 U/ml did not die of pancreatic cancer, while the 8 patients with increased CA 19-9 levels post-adjuvant therapy had a median disease-free survival of
19.6 months. In addition, a recent study that pooled individual patients’ data from 6 prospective trials found that a decline in CA 19-9 levels from baseline to after surgery and 2 rounds of adjuvant therapy was associated with a better outcome.\textsuperscript{107} In fact, increases of <5% in CA 19-9 were also associated with improved outcomes compared to patients with larger increases (OS, 10.3 months vs. 5.1 months; \( P = .002 \)).

It is important to note that CA 19-9 may be undetectable in Lewis antigen-negative individuals.\textsuperscript{118} Furthermore, CA 19-9 may be falsely positive in cases of benign or malignant biliary obstruction and do not necessarily indicate cancer or advanced disease.\textsuperscript{119,120} Preoperative measurement of CA 19-9 levels should therefore be performed after biliary decompression is complete and bilirubin is normal. If biliary decompression is not performed in a jaundiced patient, CA 19-9 levels can be assessed (category 3), but they do not represent an accurate baseline.

The panel recommends measurement of serum CA 19-9 levels prior to surgery (if bilirubin levels are normal), following surgery prior to administration of adjuvant therapy, and for surveillance (category 2B). 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.

A recent development in the field of advanced pancreatic cancer involves a potential predictive marker. Human equilibrative nucleoside transporter 1 (hENT1) is required for gemcitabine to enter cells.\textsuperscript{121} Preliminary clinical data showed that hENT1 expression levels may predict response to gemcitabine.\textsuperscript{122-124} However, results from the phase II, randomized, open-label LEAP trial, which compared a lipid-conjugated form of gemcitabine that does not require hENT1 for cell entry (CO-1.01) with gemcitabine in patients with high versus low levels of hENT1, found that hENT1 levels were not predictive for outcomes in patients treated with gemcitabine. Trial results also found no differences in outcomes between the 2 treatments in patients with low hENT2 levels.\textsuperscript{125,126} These results show that hENT1 is not a predictive marker for gemcitabine response in advanced disease.

Other potential biomarkers are also being investigated, including \textit{KRAS}, \textit{BRAF}, and \textit{SPARC}. None of these, however, have yet been validated for clinical decision making, and the panel does not recommend testing for these markers at this time.

### Differential Diagnoses

Chronic pancreatitis and other benign conditions are possible differential diagnoses of patients suspected of having pancreatic cancer.\textsuperscript{127-131} 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.\textsuperscript{129,132-134} In addition, fine-needle aspirates can be misinterpreted as malignant or suspicious for malignancies.\textsuperscript{135,136} As 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.\textsuperscript{135-138}

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.\textsuperscript{139} The classic appearance of the pancreas on abdominal CT in patients with diffuse pancreatic involvement is a
sausage-shaped enlargement of the organ with a capsule-like peripheral rim surrounding the pancreas, although focal enlargement of the pancreas is observed in some cases.\textsuperscript{133} 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, however, be negative for IgG4, thus closely mimicking pancreatic adenocarcinoma when there is a large pancreatic mass. For patients with borderline resectable disease and cancer not confirmed after 2 or 3 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.

**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.\textsuperscript{140} Early concerns about high mortality associated with various pancreatic resection procedures\textsuperscript{141} have now been lessened by studies demonstrating an acceptably low (<5%) mortality in experienced centers (see *Effect of Clinical Volume*, below).\textsuperscript{142} 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%.\textsuperscript{143} 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.\textsuperscript{144-146}

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.\textsuperscript{147-149}

The NCCN Panel recommends that decisions about diagnostic management and resectability always involve multidisciplinary consultation at high-volume centers with reference to appropriate high-quality imaging studies to evaluate the extent of disease. 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 disease involvement (pancreas and peripancreatic lymph nodes). Based on their clinical experience with the primary management of pancreatic tumors, an expert consensus group developed criteria to define tumor resectability so as to improve patient selection for surgery and increase the likelihood of an R0 resection.\textsuperscript{72,150} Other groups have also put forth definitions of resectability of pancreatic cancer.\textsuperscript{151,152} Using these criteria, tumors are classified as resectable; borderline resectable; or unresectable (ie, locally advanced or metastatic disease). Overall, the likelihood of attaining negative surgical margins (ie, R0 resection) is the key criterion for consideration when determining whether a patient is a potential candidate for resection.\textsuperscript{152,153}

In this context, a borderline resectable lesion can be defined as one in which there is a higher likelihood of an incomplete resection.

The absence of evidence of peritoneal or hepatic metastases following a thorough radiologic assessment is a criterion for both resectable and borderline resectable disease. The panel defines patients with resectable disease as those who have clear fat planes around the celiac axis, hepatic artery, and SMA and no radiologic evidence of SMV or PV distortion. On the other hand, radiologic findings of venous involvement of the SMV or PV with distortion or narrowing of the vein or occlusion of
the vein with suitable vessel proximal and distal, allowing for safe resection and replacement, characterizes a tumor as borderline resectable. As for arterial involvement, radiologic findings of 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, classifies a tumor as borderline resectable.

The consensus of the panel is that patients should be selected for surgery on the basis of curative intent as determined by the probability of obtaining R0 resection margins. Patients at high risk for positive surgical margins are not considered to be good candidates for an upfront resection. 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 Guidelines for Senior Adult Oncology for further discussion of the treatment of older patients.

**Primary Surgery for Pancreatic Cancer**

The nature and extent of the surgery for resectable tumors depend on the location and size of the tumor. Because tumors of the body and tail cause symptoms late in their development, they are usually advanced at diagnosis and are rarely resectable. When tumors in the pancreatic tail are resectable, distal pancreatectomy, in which the surgeon removes the tail and body of the pancreas, as well as the spleen, is commonly performed. If the cancer diffusely involves the pancreas or is present at multiple sites within the pancreas, a total pancreatectomy may be required, where the surgeon removes the entire pancreas, part of the small intestine, a portion of the stomach, the common bile duct, the gallbladder, the spleen, and nearby lymph nodes. Patients with tumors in the head of the pancreas, who usually present because of jaundice, are treated with open or laparoscopic pancreatoduodenectomy (ie, the Whipple procedure).

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. If a patient with jaundice is found to be unresectable at surgery, then the panel recommends stenting or biliary bypass at that time. In addition, duodenal bypass can be considered if appropriate regardless of jaundice (category 2B for prophylactic duodenal bypass). Open ethanol celiac plexus block can also be performed, especially when indicated by pain in a patient with jaundice (category 2B for a non-jaundiced patient). See Palliation of Locally Advanced and Metastatic Disease, below, for more details about these procedures.

**Pancreateoduodenectomy (Whipple Procedure)**

Achievement of a margin negative dissection must focus on meticulous perivascular dissection of the lesion in resectional procedures, recognition of the need for vascular resection and/or reconstruction, and the potential need for extra-pancreatic organ resection. Of course, the biology of the cancer might not allow for an R0 resection even with the most meticulous surgery.

Medial dissection of pancreatic head lesions is best achieved by complete mobilization of the PV and SMV from the uncinate process (assuming no evidence of tumor infiltration). Further, skeletonization of the lateral, posterior, and anterior borders of the SMA down to the level of the adventitia will maximize uncinate yield and radial margin (see Figure 1). Optimal dissection and skeletonization of the SMA can be achieved using ultrasonic or thermal dissectors (Harmonic scalpel or LigaSure). Division of the retroperitoneal tissues between the uncinate
process and the SMA with a stapler or a clamp and cut technique may leave up to 43% of the soft tissue between the uncinate process and the SMA in situ and results in suboptimal clearance and increases the risk of an R1 resection.\textsuperscript{158,159}

In the absence of frank venous occlusion noted on preoperative imaging, the need for lateral venorrhaphy or complete PV or SMV resection and reconstruction to achieve an R0 resection may be suggested, but it is often not known until division of the pancreatic neck has occurred. Tethering of the carcinoma to the lateral wall of the PV is not uncommon and requires careful dissection to free the vein from the pancreatic head if it is possible to do so. Differentiation of tumor infiltration into the vein wall from tumor-related desmoplasia is frequently impossible to ascertain. The liberal use of partial or complete vein resection when vein infiltration is suspected during Whipple procedures has been studied.\textsuperscript{160-162} On evaluation of excised vein specimens, only 60% to 70% had histologic evidence of frank tumor involvement, and R0 resections were still not obtainable in 10% to 30% of patients despite increasing the magnitude of the operative procedure. However, if an R0 resection is obtained with vein excision, longevity appears similar to those with R0 resections without venous involvement, with no significant increase in morbidity and mortality. These data support an aggressive approach to partial or complete vein excision if tumor infiltration is suspected, although acceptance of this concept (particularly with respect to vein resection) is not universal.

Although numbers are more limited, similar findings have been noted with respect to hepatic arterial resection and reconstruction.\textsuperscript{162,163} Others, however, have noted poor short- and long-term outcomes with arterial resection.\textsuperscript{164,165} While further data with respect to arterial resection are clearly needed, judicious utilization of this technique would appear to be reasonable in very select populations.

A recent population-based study of 10,206 patients from the Nationwide Inpatient Sample from years 2000 through 2009 found that vascular reconstruction (about 90% venous and 10% arterial) is associated with a higher risk of intraoperative and postoperative complications.\textsuperscript{165} No difference in mortality was seen.

**Distal Pancreatectomy**

The goals of left-sided resection are similar to those of pancreateoduodenectomy, although they are often more difficult to achieve because of the advanced stage at which most of these cancers are discovered. An R0 distal pancreatectomy for adenocarcinoma mandates en bloc organ removal beyond that of the spleen alone in up to 40% of patients.\textsuperscript{166,167} In addition, similar to the Whipple procedure, lateral venorrhaphy, vein excision and reconstruction, and dissection to the level of the celiac axis and SMA adventitia should be performed if complete tumor clearance can be achieved.\textsuperscript{167,168} Utilization of these radical resections is associated with an increase in blood loss, transfusion requirements, operating time, length of stay, and morbidity, but mortality remains rare.\textsuperscript{166-168} Encouragingly, tumor clearance (R0 resection) has been reported in up to 72% to 91% of patients, with long-term survival equivalent to those having standard resection for more localized disease.\textsuperscript{167,168} Local recurrence, however, remains problematic even with pathologically negative margins.\textsuperscript{168}

There is an increasing role for laparoscopic distal pancreatectomy. A recent metaanalysis of 4 studies of 665 total patients suggests that the laparoscopic method is safe and results in shorter hospital stays.\textsuperscript{169}

**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. 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, demonstrating that vein resection and reconstruction can allow for complete resection and is not associated with increased morbidity or mortality when compared with patients who did not require vein resection. Furthermore, long-term outcome is not significantly worse for patients undergoing venous resection during pancreatoduodenectomy compared to patients who receive standard pancreatoduodenectomy. 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. One 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. Nevertheless, a few groups have recommended caution and only use vein resection for selected patients.

Pylorus Preservation
Reconstruction options for the stomach after pancreatoduodenectomy center on preservation of the pylorus. Traverso and Longmire 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 reported no adverse effects of pylorus preservation, however, van Berge Henegouwen et al reported longer nasogastric drainage times. In several randomized and nonrandomized studies, 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.

Pancreatic Anastomosis
Efforts in this area have focused on preventing pancreatic leaks and fistulas, which are morbid and potentially lethal complications of pancreatoduodenectomy. Pancreaticojunostomy 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 pancreaticojunostomy and pancreaticogastrostomy. 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. 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. Stents used in the 1930s and 1940s continue to be used today, but data suggest that they do not decrease leak rates. Pancreatic fistula rates are similar among studies (ranging in most studies from 6% to 16%), although the exact way to define a
pancreatic leak in terms of volume and duration of drainage remains controversial. 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). Finally, the use of fibrin glue sealant does not appear to decrease the rate of pancreatic fistulas.

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. 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 SMA, and the anterior and posterior pancreatoduodenal lymph nodes. 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 PV to the origin of the inferior mesenteric artery on the left.

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. A larger randomized prospective trial was performed at Johns Hopkins Hospital from 1996 through 2001 to evaluate the role of extended lymph node dissections. 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. Recently, a randomized multicenter trial in Japan came to similar conclusions. 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. In addition, patients undergoing extended lymphadenectomy have increased rates of postoperative diarrhea compared to patients undergoing the standard resection.

The information to date thus does not show any survival advantage to performing a regional lymphadenectomy in addition to the standard pancreatoduodenectomy. At this point in time, data suggest that nodal metastases are a marker of systemic disease and that their removal is unlikely to alter OS. 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.
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 pancreatectoduodenectomy is associated with higher perioperative mortality when done in the setting of hyperbilirubinemia. 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. In 1999, a retrospective study from Memorial Sloan-Kettering Cancer Center examined 240 consecutive pancreaticoduodenectomies where 53% of patients underwent preoperative biliary decompression. 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 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; \( P < .001 \)). However, no significant differences in surgery-related complications, length of hospital stay, or mortality were observed.

Based on these reports, most groups who perform resection without neoadjuvant treatment advocate selective use of decompression only in patients who are symptomatic or septic or in whom surgical resection is significantly delayed. The panel includes in this group patients who present with jaundice and potentially resectable disease if symptoms of cholangitis or fever are present or if they have significant pruritus and an expected delay to surgery of >1 week. Most panel members endorse use of a plastic stent in these cases, since such patients may undergo surgery shortly thereafter and do 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. The University of Texas MD Anderson Cancer Center reported on its experience with more than 300 patients, 57% of whom had preoperative biliary drainage as part of a neoadjuvant chemoradiation program. It was found that wound complications were significantly increased in the drainage group; however, no other association was found for sepsis, fistulae, or death. Placement of a stent is thus required prior to administration of neoadjuvant therapy for patients with jaundice.

The panel noted 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 Palliation of Locally Advanced and Metastatic Disease, below). While any stent can become occluded, several groups have reported better patency with metal stents. 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, but the reported differences between covered and uncovered stents are not dramatic. Furthermore, migration is more of an issue with covered stents.
though these stents may still migrate in a substantial number of patients. Most metal stents used today are self-expanding. Their small initial diameters make them easy to place, and their placement rarely requires dilation. Several panel members reported that their institutions use plastic stents in patients with short life expectancies (<3 months). 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).

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 pancreatectoduodenectomy less frequently, patients might have increased morbidity and mortality. In 1993, Edge and colleagues 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. A group from Memorial Sloan-Kettering Cancer Center examined the issue in 1995 and found that in a cohort of almost 2000 patients, high-volume centers in New York State had significantly less mortality than low-volume centers (4% versus 12.3%). 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 pancreatectoduodenectomy from U.S. hospitals. 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.

The definitions of high and low volume varied among all these studies. However, a striking difference is seen when the mortality rates from pancreatectoduodenectomy in very-low-volume (0–1 procedure/year) and low-volume (1–2 procedures/year) hospitals are compared with rates in high-volume hospitals (>5 procedures/year). 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 < .001). The importance of hospital volume in improving survival after pancreatic cancer surgery is even more marked when pancreatectoduodenectomy 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 to 16 and >16 procedures per year were classified as “high” and “very-high” volume centers. 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 was seen for pancreatectoduodenectomy, 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.

Furthermore, a study involving 301,033 patients with pancreatic adenocarcinoma included in the NCDB that evaluated the treatment patterns of 1667 hospitals over a 19-year period showed that patients were more likely to receive multimodality therapy at academic institutions considered to be high-volume hospitals. In addition, a recent systematic review showed that margin status correlates with
hospital volume, with negative margin rates ranging from 55% in low-volume centers to 76% for very-high-volume centers \( (P = .008) \). This review also found that 5-year survival rates were higher in high-volume centers.

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

### Pathology

Progress in treating pancreatic adenocarcinoma is encumbered by a lack of uniformity among treating physicians in defined areas that include pathologic analysis and reporting. A more standardized approach in this area could maximize the chances of a more complete and consistent pathology report that is similar among pathologists in the same institution and among institutions around the world. Ultimately, a more consistent approach to patient assessment, surgical technique, and pathologic evaluation of the resected pancreatic specimen from gross examination to pathological report will provide better communication among the various treating physicians. It will also provide a clear and specific understanding of the individual patient’s malignancy, including critical margin status, which will then allow a more accurate comparison of the existing and evolving treatment regimens for this lethal disease.

### Lymph Node Counts

The CAP recommendations include a count of the number of lymph nodes recovered and the number of involved nodes. Recent retrospective database analyses have found that patients with N0 disease have a better prognosis with an increasing number of examined lymph nodes. These results suggest that a significant portion of patients with N0 disease might be understaged. Based on these data, groups have recommended the minimum number of lymph nodes examined be from 11 to 17 to provide optimal staging and to serve as a quality indicator.

In addition, for patients with N1 disease, lymph node ratio (positive node/nodes examined) appears to be related to prognosis. For instance, in one analysis, patients with <15% of examined positive nodes had a 5-year survival rate of 21.7%, while those with >15% positive nodes had a 5.2% 5-year survival rate \( (P = .0017) \).
Whipple Specimen

Specimen orientation and inking involves both pathologist and surgeon, as this will help to ensure accurate assessment of the size and extent of the tumor. There should be either direct communication between the surgeon and pathologist for proper orientation and margin identification, or the surgeon should identify the important margins with a clearly understood and documented method (i.e., written on the pathology requisition); for example, a stitch can be placed on the posterior margin and a safety pin on the retroperitoneal/uncinate margin.

One of the impediments to comparison of data across institutions is the variability in the names given to various margins. Definitions of the margins and uniformity of nomenclature are critical to accurate reporting. The panel’s recommended definitions are included in the Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting, section in the guidelines. Margins defined include the SMA (retroperitoneal/uncinate) margin, the posterior margin, the PV groove margin, the proximal and distal PV margins, the pancreatic neck (transection) margin, and the bile duct margin (see Figure 2). Other margins analyzed in Whipple specimens include the proximal and distal enteric margins (en face sections) and the anterior surface (closest representative). The anterior surface is not a true margin, but identification and reporting of this surface when positive may portend a risk of local recurrence, and so should be reported in all cases.\textsuperscript{245,255-257} Collectively, these pancreatic tissue surfaces constitute the circumferential transection margin. Designating the various specific margins with different colored inks will allow recognition on microscopy.

The approach to histologic sectioning of a Whipple specimen is determined by the unique characteristics of the tumor, but is also influenced by institutional preferences, expertise, and experience. Options include axial, bi- or multi-valve slicing, and perpendicular sliding (see Figure 3). Some experts in the field bisect the pancreas along probes placed in the bile and pancreatic ducts and then serially section along each half of the pancreas. Axial slicing provides an overall assessment of the epicenter of the tumor relative to the ampulla, bile duct, duodenum and pancreas, and all of the pancreatic circumferential tissue margins (see Figure 4). There is no one correct way to dissect a Whipple specimen. The most important aspects of dissection are clear and accurate assessment of the margins. It is currently unknown what constitutes an adequate margin in pancreatic carcinoma resection specimens. A standardized definition of this would allow better stratification of patients into adjuvant regimens following surgical extirpation. For instance, if less than 1-mm clearance is associated with an unacceptably high incidence of local recurrence, then strong consideration for postoperative radiation therapy (RT) might be indicated if not received preoperatively. The panel strongly recommends reporting tumor clearance in millimeters for all margins (as noted in the Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting section of the guidelines) to allow prospective accumulation of these important data for future analysis.

A recent retrospective review compared the outcomes of 169 patients with R0 resections of close margins (within 1 mm) to 170 patients with wider margins (>1 mm) and found an improvement in OS with wider margins (35 months vs. 16 months; \textit{P} < .001).\textsuperscript{258} In fact, the close-margin R0 patients had a median survival time similar to that of the R1 population (16 months vs. 14 months; \textit{P} = .6). Consistent with these results, another recent retrospective review of 285 patients found that those with R1 resections, defined as tumor \textless{}1 mm from the margin, had a significantly worse local recurrence-free survival that those with R0 resections (HR, 4.27; 95\% CI, 2.07–8.81).\textsuperscript{259,260} Together, these results
suggest that an appropriate definition of a negative margin may be >1 mm.

Attached organs resected with the specimen en bloc require serial sectioning to assess not only direct extension, but metastatic deposits as well.

**Distal Pancreatectomy Specimen**
In left-sided resections, the peripancreatic soft tissue margins and the pancreatic neck are assessed (see Figure 5). Additionally, involvement of the splenic vessels should be documented, and invasion of the spleen is important to determine, because direct tumor invasion constitutes a pT4 pathologic stage. Frozen section analysis of the pancreatic neck is recommended. Definitions of the proximal pancreatic ( transection) margin, the anterior ( cephalad) peripancreatic ( peripheral) surface, and the posterior ( caudal) peripancreatic ( peripheral) margin are included in the guidelines (see *Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting*).

**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/m² of levo-leucovorin is equivalent to 400 mg/m² 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. 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/m²) or low-dose (20 mg/m²) leucovorin. Also, the Mayo Clinic and North Central Cancer Treatment Group (NCTTG) determined that there was no therapeutic difference between the use of high- (200 mg/m²) or low- (20 mg/m²) dose leucovorin with bolus 5-FU in the treatment of advanced colorectal cancer, although 5-FU doses were different in the 2 arms. 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. In this study, patients were randomly assigned to either observation or RT combined with an intermittent bolus of 5-FU after resection. A standard split course of 4,000 cGy was used. 5-FU, 500 mg/m² 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.

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. They
found that the benefit of therapy was small in a subset of patients with pancreatic adenocarcinoma and was not statistically significant. 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 OS for the subset of patients with pancreatic cancer.

Provocative but controversial results from the European Study Group for Pancreatic Cancer (ESPAC)-1 trial have been reported by Neoptolemos and colleagues. 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. 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 RT 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; \(P < .001, \text{log rank}\)). Final results from this study showed median OS to be improved significantly for patients in the gemcitabine arm (22.8 months vs. 20.2 months; \(P = .005\)). An absolute survival difference of 12.0% was observed between the two groups at 5 years (21% vs. 9%).

The Radiation Therapy Oncology Group study RTOG 9704 was a phase III study that evaluated postoperative adjuvant treatment of resected pancreatic adenocarcinoma using either gemcitabine or fluorouracil for 3 weeks before and 12 weeks after 5-FU-based chemoradiation for both groups. This trial, which utilized daily fractionated radiotherapy, included prospective quality assurance of all patients, including central review of preoperative CT imaging and radiation fields. 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 OS 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%; \(P = .09\)); this benefit became more pronounced on multivariate analysis (HR, 0.80; 95% CI, 0.63–1.00; \(P = .05\)). The recently published 5-year analysis of RTOG 9704 showed that there was in fact no difference in OS between the two groups, although patients with tumors in the head of the pancreas showed a trend toward improved OS with gemcitabine (\(P = .08\)) upon multivariate analysis.

Whereas results from the RTOG trial suggest a possible small advantage for adjuvant therapy with gemcitabine over infusional 5-FU in patients with tumors in the pancreatic head, results from the prospective randomized trial of bolus 5-FU/leucovorin versus gemcitabine following surgery (ESPAC-3) showed no difference in OS when the 2 groups were compared (median survival was 23.0 months and 23.6 months, respectively).

Results of RTOG 9704 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 9704; and CONKO-001 excluded patients with high postoperative CA19-9 or CEA levels). However, it is interesting to note that median OS 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.

Interestingly, a recent meta-analysis of 15 prospective, randomized trials found that adjuvant chemoradiation did not improve disease-free survival, 2-year survival, or OS (odds ratio, 0.99; \( P = .93 \)), compared to surgery alone, while adjuvant chemotherapy improved all 3 outcomes (odds ratio for OS, 1.98; \( P < .001 \)). Furthermore, the multicenter, open-label, randomized phase III CapRI trial recently found that adjuvant chemoradiation with 5-FU, cisplatin, and interferon alfa-2b (IFN \( \alpha \)-2b) followed by 5-FU chemotherapy gave outcomes no better than adjuvant treatment with 5-FU alone.

Therefore, at this time, no definite standard has been established in the adjuvant treatment of pancreatic cancer. Gemcitabine- or fluoropyrimidine-based chemoradiation with additional gemcitabine, continuous infusion 5-FU, or 5-FU/leucovorin\(^{277}\) chemotherapy and chemotherapy alone with gemcitabine (category 1), 5-FU/leucovorin (category 1), or continuous infusion 5-FU 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 monotherapy is also listed in the guidelines (category 2B). The panel considered capecitabine a reasonable alternative to 5-FU/leucovorin only in this setting as a last choice in patients for whom other options are inappropriate or unacceptable. In addition, the panel recommends restaging a patient with a CT scan following systemic chemotherapy, if chemoradiation is planned.

Ongoing trials, such as ESPAC-4 (www.controlled-trials.com/ISRCTN96397434\(^{278}\)) and RTOG 0848 (ClinicalTrials.gov NCT01013649), will assess the role of gemcitabine with capecitabine, gemcitabine with erlotinib, and chemoradiation with modern chemotherapy regimens in adjuvant therapy.

**Adjuvant Treatment After Neoadjuvant Therapy**

For patients who received neoadjuvant treatment, data supporting adjuvant therapy are lacking. The consensus of the panel is that patients who have received neoadjuvant chemoradiation or chemotherapy may be candidates for additional chemotherapy following surgery and multidisciplinary review. When chemotherapy is given, the choice of regimen may be based on response seen to neoadjuvant therapy.

Adjuvant chemotherapy or adjuvant chemoradiation should only be considered for pre-treated patients who have adequately recovered from surgery and have no evidence of recurrence or metastatic disease; 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.

**Recommendations for Radiation**

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 (hepatojejunosotomy and gastrojejunosotomy may be omitted if clinically appropriate), 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.\textsuperscript{280,281} 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, 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.\textsuperscript{274,280,282}

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.\textsuperscript{283} 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 9704 trial.\textsuperscript{274,284} Comparing the 2 trials, rates of grade 3/4 nausea and vomiting were 0\% vs. 11\% (\textit{P} = .024), and rates of grade 3/4 diarrhea were 3\% vs. 18\% (\textit{P} = .017),\textsuperscript{284} suggesting that IMRT may be well tolerated and allow for higher radiation doses to the tumor.\textsuperscript{284} 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.\textsuperscript{285,286} 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 OS.\textsuperscript{287,288} The putative benefits of neoadjuvant therapy include increasing the likelihood that a higher proportion of resectable patients will receive chemotheraphy and/or radiation; the potential to downsize tumors so as to increase the likelihood of a margin-free resection (ie, conversion to resectable status); 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.\textsuperscript{152,289-291} Moreover, surgery following neoadjuvant treatment appears to be safe.\textsuperscript{292,293}

EUS with FNA is the preferred method of obtaining histologic confirmation of disease, and such confirmation is necessary before administering neoadjuvant therapy. A repeat biopsy should be performed in cases where the initial biopsy results do not confirm cancer. In addition, staging laparoscopy, performed to evaluate for the possible presence of metastatic disease, can be considered before and after neoadjuvant therapy. Furthermore, patients for whom neoadjuvant therapy is planned should be assessed for jaundice, and placement of a stent (preferably a short metal stent) is recommended prior to initiation of neoadjuvant therapy in patients with jaundice.\textsuperscript{223-225}

There is insufficient evidence to recommend specific neoadjuvant regimens, and practices vary with regards to chemotherapy and chemoradiation. Most published neoadjuvant regimens incorporate RT, although chemotherapy alone is currently being evaluated. Neoadjuvant therapy regimens are often similar to those used to treat locally...
advanced disease (see Chemoradiation for Locally Advanced Disease, below), and include upfront continuous infusion 5-FU- or capecitabine-based chemoradiation,^{291,294} upfront gemcitabine-based chemoradiation,^{295} or induction chemotherapy followed by 5-FU- or gemcitabine-based chemoradiation.^{224} Options for radiation include 45-54 Gy in 1.8-2.5 Gy fractions or 36 Gy in 2.4 Gy fractions.^{296} Doses higher than 54 Gy may be considered if clinically appropriate. 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 is ideally performed 4 to 8 weeks after therapy. Surgery can be performed more than 8 weeks following therapy, but radiation-induced fibrosis may potentially make surgery more difficult.

Neoadjuvant Therapy in Resectable Disease

A number of studies have evaluated the use of neoadjuvant chemoradiation in patients with resectable disease.^{288,289,296-304} 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. 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 that would not benefit them. In this analysis of 132 consecutive patients, the authors 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. The MD Anderson group has continued to champion this approach both for its ability to select patients for resection and for cost-effectiveness.^{305} Other potential advantages of the neoadjuvant approach in resectable patients have also been described, including sterilization of the field before resection potentially reducing spread during surgery; increased rates of R0 resections; decreased incidence of pancreatic fistulas; prevention of delays or reductions of adjuvant therapy after surgery; and improved delivery of chemotherapy and radiosensitizing oxygenation.^{293,306,307}

Although most studies investigating the neoadjuvant experience in patients with pancreatic cancer are retrospective, several small phase II studies have been published.^{293,306,308,309} 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 gemcitabine with cisplatin were able to undergo resection compared with those in the gemcitabine-only arm.^{303} 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. Although all patients were able to complete neoadjuvant therapy, at the time of restaging, only 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. 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. 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, results of randomized trials addressing this issue have yet to be reported. A phase III trial with a PFS endpoint comparing adjuvant therapy with a combination of neoadjuvant and adjuvant therapy is currently recruiting patients (ClinicalTrials.gov NCT01314027). A phase II trial with R0 resection as the primary endpoint is ongoing (ClinicalTrials.gov NCT01389440).

At this time, the panel does not recommend neoadjuvant therapy for most resectable patients, except on a clinical trial. For selected patients who appear technically resectable but have poor prognostic features, however, consideration can be given to neoadjuvant therapy after biopsy confirmation, though a clinical trial is still preferred.

**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 Member Institutions prefer an initial approach involving neoadjuvant therapy, as opposed to immediate surgery, for patients with borderline resectable disease. Furthermore, the panel considers neoadjuvant therapy as an acceptable option to upfront resection following clinical staging of disease as borderline resectable.

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. A randomized phase II trial comparing 2 different neoadjuvant regimens in borderline resectable disease was terminated early due to poor accrual, but 5 of 21 patients (24%) were resected. In 2 recently published retrospective reviews, 31% to 35% of borderline resectable patients who completed neoadjuvant therapy had R0 resections. A recent systematic review and meta-analysis of 19 cohort studies found that unresectable patients (including both borderline and unresectable patients) undergoing neoadjuvant chemoradiation therapy had similar 1-year survival outcomes as patients who were initially deemed resectable. In this study, 40% of treated patients were ultimately resected.

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 the best regimens to use in the borderline neoadjuvant setting are unknown. Several phase II clinical trials are currently underway to determine the R0 resection rate following neoadjuvant chemotherapy in patients with borderline resectable or unresectable locally advanced disease (eg, ClinicalTrials.gov NCT00557492 and NCT01359007). In addition, the Alliance A021101 trial is a single-arm pilot study evaluating the safety and efficacy of FOLFIRINOX before capecitabine-based chemoradiation and surgery in this population. Additional randomized trials are needed.

**Recurrent Disease**

As cross-sectional body imaging has improved, small-volume metastatic disease or local recurrence is being detected in patients with pancreatic cancer who are otherwise maintaining good functional status. As many as 50% of them will continue to maintain a sufficiently good
Chemotherapy for Locally Advanced or Metastatic Disease

Systemic therapy is used 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 Guidelines for Supportive Care, available at www.NCCN.org). 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, as decreased oral intake, and as constipation.
For patients who derive clinical benefit from initial chemotherapy treatment in the setting of locally advanced disease without developing distant disease, subsequent chemoradiation may enhance local control (see Chemoradiation for Locally Advanced Disease, below).

It is important to reiterate that biopsy confirmation of pancreatic adenocarcinoma be obtained before treatment. At least 2 or 3 negative or indeterminate 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.

Leucovorin Shortage

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

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/leucovorin plus oxaliplatin and irinotecan (FOLFIRINOX) for the treatment of patients with metastatic solid tumors. Their study included 2 patients with pancreatic cancer, and the regimen showed anti-tumor activity. A subsequent multicenter phase II trial specifically for patients with advanced pancreatic adenocarcinoma demonstrated promising response rates. A later randomized phase II trial showed a response rate of >30% to FOLFIRINOX in patients with metastatic pancreatic cancer.

Results from the randomized phase III PRODIGE trial evaluating the regimen of FOLFIRINOX versus gemcitabine alone in patients with metastatic pancreatic cancer and good performance status showed dramatic improvements in both median progression-free survival (6.4 months vs. 3.3 months; \(P < .001\)) and median OS (11.1 months vs. 6.8 months; \(P < .001\)), in favor of the group receiving FOLFIRINOX. Because of these strong results, the panel added FOLFIRINOX as a category 1 recommendation for first-line treatment of good performance status patients with metastatic pancreatic cancer in 2011. It is listed as a category 2A recommendation for patients with locally advanced unresectable disease by extrapolation.

There are, however, some concerns about the toxicity of the FOLFIRINOX regimen. In the PRODIGE trial, some of the grade 3/4 toxicity rates that were significantly greater in the FOLFIRINOX group than in the gemcitabine group were 45.7% for neutropenia, 12.7% for diarrhea, 9.1% for thrombocytopenia, and 9.0% for sensory neuropathy. Despite the high levels of toxicity, no toxic deaths have been reported. Furthermore, the PRODIGE trial determined that, despite this toxicity, fewer patients in the FOLFIRINOX group than in the gemcitabine group experienced a degradation in their quality of life at 6 months (31% vs. 66%, \(P < .01\)). A more detailed analysis of the quality of life of patients in this trial has been published and shows that FOLFIRINOX maintained and even improved quality of life more than gemcitabine did.

A phase II trial studying FOLFIRINOX as a possible conversion therapy is currently recruiting patients to assess the proportion of patients that can be converted to resectable status and undergo R0 resections (clinical.trials.gov NCT01359007).

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.
recommends gemcitabine monotherapy as one option for front-line therapy for patients with metastatic disease (category 1). The NCCN Panel also recommends gemcitabine monotherapy as an option for patients with unresectable, locoregional disease (category 2A).

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) maximizes intracellular concentrations of the phosphorylated forms of gemcitabine.\(^{327}\) 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.\(^{328}\) 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; \(P = .04\)), although this outcome did not satisfy the protocol-specified criteria for superiority.\(^{329}\) When gemcitabine is considered for the treatment of advanced pancreatic cancer, the NCCN Panel views FDR gemcitabine (10 mg/m\(^2\)/min) as a reasonable alternative to the standard infusion of gemcitabine over 30 minutes (category 2B).

FDR gemcitabine is incorporated into some commonly used gemcitabine-based regimens (eg, GEMOX [gemcitabine, oxaliplatin] and GTX [gemcitabine, docetaxel, and capecitabine], see Gemcitabine Combinations below).\(^{330,331}\) The combination of FDR gemcitabine and capecitabine has also been found to be active and well tolerated.\(^{332}\)

**Gemcitabine Combinations**

The NCCN Panel 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 endpoints 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, 5-FU).\(^{329-331,333-343}\) Two recent meta-analyses of randomized controlled trials both found that gemcitabine combinations give a marginal benefit in OS over gemcitabine monotherapy, with a significant increase in toxicity.\(^{344,345}\)

Recommended combinations are discussed below. The panel does not consider the combination of gemcitabine plus docetaxel\(^{346}\) or gemcitabine plus irinotecan\(^{343,346,347}\) to meet the criteria for inclusion in the guidelines. In addition, gemcitabine plus sorafenib is not recommended. The recent multi-center, double-blind, placebo-controlled, randomized phase III BAYPAN trial compared gemcitabine plus either sorafenib or placebo in chemotherapy-naïve patients with advanced or metastatic disease.\(^{348}\) This trial did not meet its primary endpoint of PFS in its 104 patients (5.7 months vs. 3.8 months; \(P = .90\)).

**Gemcitabine Plus Nab-Paclitaxel**

Nab-paclitaxel is an albumin-bound nanoparticle form of paclitaxel. In a publication of a phase II/III trial, 67 patients received gemcitabine plus
nab-paclitaxel. At the maximum tolerated dose, the partial response rate was 48%, with an additional 20% of patients demonstrating stable disease for ≥16 weeks. The median OS at this dose was 12.2 months.\(^{349}\)

Based on these results, the large, open-label, international, randomized phase III MPACT trial was initiated in 861 patients with metastatic pancreatic cancer and no prior chemotherapy.\(^{350}\) Participants were randomized to receive gemcitabine plus nab-paclitaxel or gemcitabine alone. The trial met its primary endpoint of OS (8.5 months vs. 6.7 months; \(P < .001\); HR, 0.72; 95% CI, 0.62–0.84).\(^{350}\) The addition of nab-paclitaxel also improved other endpoints, including 1-year survival, 2-year survival, response rate, and PFS. The most common grade 3 or higher adverse events attributable to nab-paclitaxel were neutropenia, fatigue, and neuropathy.

For the 2013 guidelines, the panel upgraded the combination of gemcitabine plus nab-paclitaxel from a category 2B to a category 1 recommendation for the treatment of patients with advanced disease and good performance status based on these results.

**Gemcitabine Plus Erlotinib**

Although phase II trial results of gemcitabine combined with new targeted drugs (eg, bevacizumab, cetuximab) were encouraging,\(^{351,352}\) 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.\(^{353-357}\) Results of the CALGB phase III trial, which evaluated gemcitabine and bevacizumab (an anti-vascular endothelial growth factor [VEGF] 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.\(^{354,355}\) In a phase III trial comparing gemcitabine and erlotinib with or without bevacizumab in patients with metastatic pancreatic cancer, bevacizumab did not improve OS, although a significant improvement in progression-free survival was observed with the addition of bevacizumab to the gemcitabine/erlotinib combination.\(^{357}\) A recent randomized phase III trial of another VEGF inhibitor, axitinib, in combination with gemcitabine also failed to show any improvement in OS of patients with advanced pancreatic adenocarcinoma.\(^{356}\)

In contrast, in the phase III, double-blind, placebo-controlled NCIC CTG PA.3 trial of 569 patients 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 OS (HR, 0.82; \(P = .038\)) and progression-free survival (HR, 0.77; \(P = .004\)) when compared to patients receiving gemcitabine alone.\(^{353}\) 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.\(^{355}\) This trial, other trials, and community experience show that occurrence of grade 2 or higher skin rash is associated with better response and OS of patients receiving erlotinib.\(^{353,358,359}\)

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). However, the panel notes that although this combination significantly improved survival, the
actual benefit was small, suggesting that only a subset of patients benefit.

**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.334,335,338 Nevertheless, selected patients may benefit from this regimen because patients with breast and ovarian cancers who are carriers of a **BRCA** mutation360,361 and selected patients with inherited forms of pancreatic cancer44 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.362 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 < .01).362 Furthermore, in a recent report, 5 of 6 patients with known **BRCA** mutations and metastatic pancreatic adenocarcinoma treated with a platinum-based regimen at Memorial Sloan-Kettering Cancer Center showed a radiographic partial response.363 Thus, 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.333 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 OS for the combination arm did not reach statistical significance.336 Similarly, results from another smaller phase III trial evaluating this combination did not demonstrate an OS advantage for overall study population receiving the combination of gemcitabine with capecitabine, although a post-hoc analysis showed OS to be significantly increased in the subgroup of patients with good performance status.340 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.364 Of note, results from several studies have indicated that the benefit of gemcitabine combination chemotherapy is predominantly seen in patients with good performance status.337,338,340

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.

**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. 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% having grade 3/4 anemia. A recent retrospective case-review study at Johns Hopkins Sidney Kimmel Comprehensive Cancer Center found similar results, with a median OS of 11.6 months and grade 3 or greater hematologic and non-hematologic toxicity rates of 41% and 9%, respectively.

**Capecitabine and Continuous Infusion 5-FU**
The panel lists capecitabine monotherapy and continuous infusion 5-FU as first-line treatment options for patients with locally advanced unresectable or metastatic disease (category 2B). The capecitabine recommendation is supported by a randomized phase III trial from the Arbeitsgemeinschaft Internistische Onkologie (AIO) group in which OS was similar in patients with advanced pancreatic cancer receiving capecitabine plus erlotinib followed by gemcitabine monotherapy or gemcitabine plus erlotinib followed by capecitabine monotherapy.

**Fluoropyrimidine Plus Oxaliplatin**
The combination of a fluoropyrimidine (5-FU/leucovorin or capecitabine) with oxaliplatin is also listed as a possible first-line treatment for metastatic or locally advanced disease (category 2B). The panel bases these recommendations on the randomized phase III CONKO-003 trial (5-FU/leucovorin/oxaliplatin vs. best supportive care) and on a phase II study (CapeOx). Both of these studies only enrolled patients who had received 1 prior chemotherapy regimen, but the panel feels the extrapolation to first-line therapy is appropriate (category 2B).

**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. It is used in selected patients who do not develop metastatic disease during initial chemotherapy and occasionally before chemotherapy. The role of chemoradiation was initially defined in a trial conducted by GITSG. In this study, the combination of bolus 5-FU and split-course radiation (total dose, 4000 cGy) was compared with radiation alone or with 6000 cGy combined with 5-FU. A nearly 2-fold increase in median survival (42.2 vs. 22.9 weeks) was observed with the regimen of bolus 5-FU and 4000 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. Evidence suggests that concurrent gemcitabine and radiation can yield similar or better outcomes when compared with 5-FU-based chemoradiation. The use of capecitabine as a radiosensitizer has also been assessed and appears to be effective.
Chemotherapy without RT is also an option for patients with locally advanced pancreatic cancer, especially for patients with poor performance status. Results of 2 randomized trials comparing chemoradiation to chemotherapy in locally advanced disease were contradictory.\textsuperscript{377,378} The phase III randomized ECOG-4201 trial, which assessed gemcitabine compared with gemcitabine plus RT followed by gemcitabine alone in patients with locally advanced, unresectable pancreatic cancer, was closed early due to poor accrual. However, an ITT analysis of data for the 74 patients enrolled in this study showed that median OS was significantly longer in the chemoradiation therapy arm of the study (11.1 months vs. 9.2 months; \(P = .017\)).\textsuperscript{379} However, the poor accrual rate decreased its statistical power, there was no difference in progression-free survival, and the confidence intervals for OS overlapped between the two groups of patients, leading some to state that the results do not rise to the level of evidence required to determine standard of care.\textsuperscript{380}

The benefit of chemotherapy versus chemoradiation was also addressed in the phase III FFCD-SFRO study from France, in which patients with locally advanced pancreatic cancer were randomly assigned to receive either gemcitabine alone or an intensive induction regimen of chemoradiation with 5-FU plus cisplatin followed by gemcitabine maintenance treatment.\textsuperscript{381} In this study, gemcitabine alone was associated with a significantly increased OS rate at 1 year compared with chemoradiation (53\% vs. 32\%; HR, 0.54; 95\% CI, 0.31–0.96; \(P = .006\)). 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.

### Chemotherapy or Chemoradiation as Conversion Therapy

Some studies and case reports have addressed the use of chemotherapy with or without chemoradiation to convert selected patients with locally unresectable disease to a resectable status.\textsuperscript{287-289,291,382-385} Patients with a significant response to chemotherapy and/or chemoradiation may be considered for surgical resection. Following resection, these patients have similar survival rates as those initially determined to be resectable.\textsuperscript{386}

### Recommendations for Chemoradiation

Starting with 2 to 6 cycles of systemic chemotherapy (see Chemotherapy for Locally Advanced or Metastatic Disease, above) followed by chemoradiation therapy is an option for select patients with unresectable disease and good performance status who have not developed metastatic disease.\textsuperscript{387-389} This sequence is especially recommended in cases where: 1) it is highly unlikely that the patient will become resectable (ie, complete encasement of superior mesenteric/ceci alaneries); 2) there are suspicious metastases; or 3) the patient may not be able to tolerate chemoradiation. If patients present with poorly controlled pain or local obstructive symptoms, however, it may be preferable to start with upfront chemoradiation therapy.\textsuperscript{369,371} 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.\textsuperscript{369,390-392} 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 outcomes 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.\textsuperscript{387}

Following an adequate course of chemotherapy, laparoscopy is performed as indicated to evaluate distant disease. The panel also recommends restaging with a CT scan at this time. The panel recommends chemoradiation for patients with locally advanced unresectable disease and good performance status who did not develop metastases during initial treatment. If patients develop metastatic disease during systemic chemotherapy, chemoradiation is not given unless required for palliation. Patients should be evaluated for recovery from hematologic and non-hematologic toxicity prior to initiation of chemoradiation. Following chemoradiation therapy, additional maintenance chemotherapy is sometimes used, especially if tumors are still unresectable.

Radiation is given with concurrent gemcitabine,\textsuperscript{224,295,369-373,393} capecitabine, or continuous infusion 5-FU.\textsuperscript{368} For primary definitive chemoradiation therapy, 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.\textsuperscript{372} 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).

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.\textsuperscript{394-396} A retrospective treatment planning study evaluated the dose escalation that might have been possible in 15 patients with locally advanced unresectable pancreatic adenocarcinoma if IMRT had been used instead of 3-D conformal planning.\textsuperscript{396} 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, 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 demonstrated that while SBRT gave effective local control, it gave no improvement to OS and was associated with significant toxicities.\textsuperscript{397} However, another retrospective review of 71 patients reported a median OS of 10.3 months with only 3 patients (4%) experiencing grade 3 toxicity.\textsuperscript{398} There is 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.

Second-Line Therapy

For patients who have received prior gemcitabine-based therapy, fluoropyrimidine-based chemotherapy regimens are acceptable second-line options.\textsuperscript{319,320,399} The panel includes capecitabine, 5-FU/leucovorin/oxaliplatin,\textsuperscript{319} and CapeOx\textsuperscript{320} as options. Note that the capecitabine dose recommended in the guidelines (1000 mg/m\textsuperscript{2} PO twice daily) 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).\textsuperscript{400}

Chemoradiation can also be given as salvage therapy in patients with locally advanced unresectable disease if it was not previously given and if the primary site is the sole site of progression.

Of note, results from the phase III CONKO-003 trial presented in 2008 showed significant improvements in both median progression-free
survival (13 weeks vs. 9 weeks; \( P = .012 \)) and median OS (20 weeks vs. 13 weeks; \( P = .014 \)) when oxaliplatin was added to 5-FU/leucovorin,\(^{401,402} \) making this regimen the standard approach for second-line therapy for patients without prior exposure to fluoropyrimidine-based therapy. Recently published results from this trial demonstrated the superiority of 5-FU/leucovorin/oxaliplatin over best supportive care in both median second-line survival (4.8 months vs. 2.3 months; \( P = .008 \)) and median OS (9.1 months vs. 7.9 months; \( P = .031 \)).\(^{319} \)

The AIO-PK0104 trial also assessed second-line therapy in a randomized cross-over trial and found capecitabine to be an efficacious salvage treatment after progression on gemcitabine/erlotinib in patients with advanced disease.\(^{403} \) In this trial, capecitabine/erlotinib followed by gemcitabine gave similar outcomes to the aforementioned sequence.

**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 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.\(^{404} \)

- 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 that 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 OS.
- Quality control standards for preoperative imaging interpretation, pathologic assessment of tumor specimens, and surgical selection criteria are critical when evaluating adjuvant therapies.

A more recent consensus report from a group of European experts came to many of the same conclusions.\(^{405} \) Additionally, the group
states that FOLFIRINOX can be considered as a new standard treatment option in selected patients in future clinical trials, but that gemcitabine should remain the standard for most patients. An international expert panel also met recently to discuss current and future pancreatic cancer research and came to similar conclusions. In addition, the Intergroup Pancreatic Cancer Task Force’s Tissue Acquisition Working Group has made recommendations regarding the prospective collection and sharing of tissue to accelerate the discovery of predictive and prognostic biomarkers. These recommendations include centralization of biorepositories and mandatory collection of tissue (when there is sufficient material), blood, serum, and plasma in all phase III trials.

**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% to 75% of patients with pancreatic cancer develop symptomatic biliary obstruction. For patients diagnosed with unresectable disease and biliary obstruction upon initial evaluation, the best palliation is provided by an endoscopic biliary stent, especially when anticipated survival is limited. In most cases, a permanent self-expanding metal stent (SEMS) is 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-known complication of plastic (temporary) biliary stents and typically occurs within 3 months of insertion. Metal stents are wider in diameter than plastic 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 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 ($P = .002$), respectively. A meta-analysis comparing metal and plastic biliary stents placed endoscopically in patients with pancreatic adenocarcinoma characterized by biliary obstruction showed similar results. 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 past the neoplasm that is obstructing the gastric outlet), percutaneous biliary drainage with subsequent internalization may be necessary. An alternative is to sequentially dilate the duodenum endoscopically, place a metallic biliary stent, and then place an enteral stent. Durable palliation of biliary obstruction can often be achieved with an expandable metallic biliary endoprosthesis (eg, Wallstent, Boston Scientific) in this situation.

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
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recommends stenting or an open biliary-enteric bypass with or without duodenal bypass (category 2B for prophylactic duodenal bypass\(^{411,412}\)) and with or without open ethanol celiac plexus block\(^{413-415}\) (category 2B in non-jaundiced patients). Please see Gastric Outlet Obstruction and Severe Tumor-Associated Abdominal Pain below for more detailed information on these procedures. 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.\(^{407}\)

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\(^{411,412}\)) 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 (those for whom surgical resection will not be attempted). In this situation, a SEMS 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 because of the lack of concern about long-term patency. If cancer has not been biopsy-confirmed in the setting of locally advanced disease in a jaundiced patient, brushings can be obtained at the time of stent placement (short metal stent preferred in this situation).

Gastric Outlet Obstruction
Symptomatic gastric outlet obstruction occurs in 10% to 25% of patients with pancreatic cancer.\(^{407}\) 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.\(^{410}\) An alternative for these patients 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 (ie, locally advanced disease) who develops gastric outlet obstruction, an open or laparoscopic gastrojejunostomy (duodenal bypass) 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.\(^{416-418}\) 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 prophylactic gastrojejunostomy should be performed for those deemed to be at risk of developing symptomatic gastric outlet obstruction (category 2B). 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.\(^{411,412}\) In both studies, approximately 20% of patients who did not undergo a prophylactic gastrojejunostomy developed late gastric outlet obstruction that required therapy. A recent meta-analysis found similar results, with development of gastric outlet obstruction in 2.5% of patients in the prophylactic gastrojejunostomy group and 27.8% of those not receiving gastrojejunostomy.\(^{419}\) 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.
Severe Tumor-Associated Abdominal Pain

Most patients with locally advanced or metastatic pancreatic cancer experience cancer-related pain. General principles for cancer-related pain management can be found in the NCCN Guidelines for Adult Cancer Pain (available at www.NCCN.org). Because advanced pancreatic cancer often infiltrates the retroperitoneal nerves of the upper abdomen, open ethanol celiac plexus neurolysis should be considered (category 2B, except when indicated by pain in a jaundiced patient who is found unresectable at surgery, for which the recommendation is a category 2A). In 2 randomized controlled trials, celiac plexus neurolysis significantly improved pain relief in patients with advanced pancreatic cancer. In a recent study of 96 patients with pain related to suspected pancreatic cancer, half were randomized to EUS-guided celiac plexus neurolysis at the time of EUS if unresectable adenocarcinoma was confirmed. These patients reported better pain relief at 3 months (P = .01), suggesting that early EUS-guided celiac plexus neurolysis may be beneficial. 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.

In selected patients with severe local back pain refractory to narcotic therapy, palliative RT 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 25–36 Gy in 2.4–5 Gy fractions), or radiation alone is given to the metastatic site.

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. This deficiency in pancreatic enzymes results in inadequate absorption of fat, carbohydrates, and proteins, leading to steatorrhea, abdominal cramps, weight loss, and malnutrition. 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, therapy may be initiated without diagnostic tests. Enteric-coated mini-microspheres containing preparations of pancreatic enzymes are taken orally (25,000–75,000 units of lipase for a main meal and 10,000–25,000 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 the middle of the meal. 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. Patients with a clinical suspicion of pancreatic insufficiency despite appropriate replacement may need a more thorough nutritional evaluation.

Thromboembolic Disease

The risk of developing venous thromboembolic disease is substantially increased in patients with pancreatic cancer. 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. 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. 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, and Malnutrition**

For many patients, a diagnosis of pancreatic cancer may result in significant psychosocial distress, including anxiety, depression, and sleep disturbances. In fact, the suicide rate in male patients with pancreatic cancer is reportedly 11 times that of the general population. Empathetic discussion about the natural history of this disease and its prognosis and the provision of support and counseling both by the primary oncology team and specialized services may help to alleviate this distress. The panel recommends that patients be screened and evaluated for depression and other psychosocial problems following the NCCN Guidelines for Distress Management (available at www.NCCN.org).

Because pain and malnutrition are also prevalent in patients with pancreatic cancer, the panel recommends that patients with locally advanced or metastatic pancreatic cancer receive a nutritional evaluation and a formal evaluation by a Palliative Medicine Service, when appropriate. Additional resources are detailed in the NCCN Guidelines for Palliative Care and the NCCN Guidelines for Adult Cancer Pain (available at www.NCCN.org).

**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. In fact, a recent analysis of the SEER-medicare database showed no significant survival benefit for patients who received regular surveillance CT scans.

**Summary**

Resection remains the only chance for a cure of pancreatic adenocarcinoma, and most resectable patients should undergo surgery without delay, followed by adjuvant therapy. Borderline resectable patients and select resectable patients can undergo neoadjuvant therapy in the hopes of improving the chances for an R0 resection or can immediately undergo surgery. Salvage therapy is an option for those patients whose disease recurs following surgery. Patients with locally advanced unresectable disease and good performance status can undergo chemotherapy and chemoradiation with second-line therapy if performance status is maintained after progression. Good performance status patients presenting with metastatic disease can undergo chemotherapy and can undergo second-line therapy if performance status is maintained after progression. 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.

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.
Figure 1. Complete mobilization of the superior mesenteric (SMV) and portal veins, and separation of the specimen from the right lateral border of the superior mesenteric artery (SMA).
Figure 2. Whipple specimen with labeled margins.
Figure 3. Slicing of pancreatoduodenectomy specimens.
Figure 4. Slicing of the pancreatoduodenectomy specimen in the axial plane to allow circumferential assessment of tumor.
Figure 16-4, from Hruban, Ralph et al. Tumors of the Pancreas: Afip Atlas of Tumor Pathology, American Registry of Pathology, Washington DC 2007

Figure 5. Slicing of the distal pancreatectomy specimen.
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